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PROBLEMS RELATING TO THE INVASIVE PROPERTIES OF HEMOLYTIC STREPTOCOCCI AND THEIR CONTROL BY SULPHANILAMIDE.*

By Warfield T. Longcope, M.D.,

PROFESSOR OF MEDICINE, SCHOOL OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MD.

(From the Medical Clinic of the School of Medicine, Johns Hopkins University and Hospital.)

The remarkable results that have been obtained recently in the treatment, by chemotherapy, of hemolytic streptococcal infections, form an incentive to study with renewed vigor many problems relating to the invasive properties of hemolytic streptococci, and to the resistance of the body against this organism.

The hemolytic streptococcus has peculiarities that distinguish it from other known bacteria. One of its striking attributes is its ability to cause infections of the most varied character. In the first place, it is well known that a small number of people harbor, from time to time, hemolytic streptococci in their fauces or tonsils. It has been estimated that during the winter months in New York and Baltimore 9% to 14% of normal individuals are temporary carriers of this organism.[6,40a,56,71] A few persons may persistently carry the organism in their fauces. When, however, the hemolytic streptococcus actually invades the body, it may give rise in some patients to a comparatively benign local infection of the skin, or a mild tonsillitis; in others, it may cause such specific diseases as scarlet fever or erysipelas; in a third, it may produce a fulminating general septicemia following an insignificant local lesion, or fatal meningitis complicating mastoiditis. It is particularly prone to invade tissues made susceptible by some comparatively benign disease such as

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measles or influenza, and may convert epidemics of these infections into veritable plagues.

Most of the local infections, except, of course, those that involve the serous surfaces, are sometimes so mild as to be almost insignificant; but, on the other hand, any one of them may assume such a virulent character as to be fatal almost within a few hours.

The greatest dangers in any form of streptococcal infection come from a spread of the process locally, or an invasion of the blood stream. The character, form, severity, and outcome of the infection must depend upon the portal of entry, the virulence of the infecting organism, and the degree to which the patient is able to marshal together his forces of defense.

It is not necessary to dwell upon the variations in the form of the infection that depends upon the portal of entry of the organism for it is obvious that when hemolytic streptococci are introduced into the skin the clinical characteristics of the disease that follows are totally different from those resulting from contamination of the uterine canal or infection of the throat.

The infections in man are due principally, though not exclusively, to hemolytic streptococci belonging to the Lancefield Group A.[38b] Occasionally, members of other groups, notably the minute hemolytic streptococci of Long and Bliss,[4] which are included by Lancefield in Group F, cause infections in man, while anerobic hemolytic streptococci are frequently found in lung abscesses (Fisher[21]) and may cause puerperal sepsis.

Type specific strains of hemolytic streptococci are recognizable within Group A (Griffith,[30] Lancefield[38a]) and localized epidemics have been traced to a single specific type (Griffith,[30] Swift, Lancefield and Goodner).[65] The infections occurring in these epidemics are, however, of various forms, and up to the present time it has not been possible to demonstrate conclusively that scarlet fever and erysipelas, which represent highly differentiated forms of streptococcal infections, are caused regularly by a single specific strain of hemolytic streptococcus, though a limited number of Griffith's 20 types have been obtained from epidemics of scarlatina,[30] and by Pauli and Coburn[53] from infections of the throat preceding attacks of rheumatic fever. In this respect, the situation seems to be analogous to that which exists in lobar pneumonia or in epidemic meningitis.

Strains of hemolytic streptococci belonging to the Lancefield Group "A" produce substances some of which are certainly injurious to the host. Among these are the erythrotoxins, which are familiar as causing the skin reaction, the hemolysins, extensively studied by Todd,[68a,b] fibrinolysin described by Tillett and Garner,[67a,b] leukocidin and the toxic material extracted from hemolytic streptococci by Weld.[72] It is probable that the spreading factor of Duran-Reynolds,[18a,b] which may be derived from the bacteria themselves,

a somewhat similar substance obtained by Vally Menkin[46] from inflammatory exudates, and the fibrinolytic property of the organism, are largely responsible for the advance of the infection through tissues.

Soluble antibodies to these noxious substances are formed by the host, but their importance in combating the infection during its early stages, and the part which they play in bringing about recovery is not entirely clear. The bactericidal property of the blood for hemolytic streptococci may be much increased during these infections. When the infection remains localized, however, the increase, according to Hare[32] may only be demonstrated during convalescence, or may not appear at all. If the infection becomes generalized, on the other hand, there is an early and marked increase in the bactericidal property of the blood, not only in those patients who recover, but in about half of those who succumb to the infection. Keefer, Ingelfinger, and Spink[36] have been able to confirm these observations. Hare believes he can show that the increased bactericidal property of the blood is due partly to a bacteriostatic or bactericidal property of the serum and partly to the formation of bacteriotropins which bring about an increase in the amount of phagocytosis, even though the leukocytes may actually have sustained some injury. In this particular, and perhaps highly important, protective mechanism, one must take into account the activities of the cells of the body as well as the property of the serum.

During one phase or another of the infection, specific agglutinins and precipitins; antihemolysin and antifibrinolysin as well as neutralizing substances to the erythrotoxin (scarlatina), may be demonstrated in the serum. And finally, following repeated infections by hemolytic streptococci, the skin of an individual may become highly sensitive to the nucleo-protein of the hemolytic streptococcus or to the products of its growth.

It is probable, therefore, that the variety, the special character, the severity, and the outcome of infections by hemolytic streptococci are determined by many factors. The disease will depend on the one hand upon the predominance of one or another of the biologic properties of the infecting organism and on the other upon the varying states of resistance or susceptibility, immunity, or allergy that modify the responses to infection in the host. It is the interaction of these forces that is responsible for the variegated clinical pictures in streptococcal infections, and that renders their course, to say the least, kaleidoscopic.

As examples, one may mention scarlet fever, in which the rash and early intoxication are presumably caused by circulating toxins while the complications, such as adenitis, meningitis, or arthritis are due to an invasion of the tissues by the bacteria themselves. After recovery, an immunity to the erythrotoxin protects against second attacks of scarlatina, but not against subsequent and often

serious infections by hemolytic streptococci. Erysipelas, on the other hand, is characterized by a local spreading infection which endangers the life of the patient by invasion of tissues or by extension of hemolytic streptococci into the blood stream. Recovery is often followed by subsequent attacks. This susceptibility to repeated attacks of erysipelas has been attributed to the development of an allergic state towards hemolytic streptococci or to the products of their growth. Still further variations occur, for a slight infection of the skin may be followed almost immediately by a rapidly fatal septicemia, as another example, or a mild attack of pharyngitis or tonsillitis may be complicated by acute hemorrhagic nephritis with violent onset, or by an exacerbation of rheumatic fever.

When we search for criteria to measure the progress of streptococcal infections it is found that a continuous local spread of the infection and an invasion of the blood by hemolytic streptococci are two particularly unfavorable signs. We have been interested for some time in the latter problem and have analyzed 166 cases of hemolytic streptococcal septicemia gathered largely from the adult services at this hospital in order to gain information about the types of infection in which an invasion of the blood is most likely to occur and to learn what the ultimate outcome may be in these patients.*

It is well known that septicemia due to hemolytic streptococci results fatally in a large proportion of cases. Of the 166 cases that I have analyzed 125 died, a fatality rate of 75.3%. This corresponds almost exactly with the figure given by Keefer, Ingelfinger, and Spink,[36] who in a series of 246 patients found the mortality to be 72%. An invasion of the blood, however, is not of equally serious significance in all forms of infections. This is shown in the accompanying Table 1, where it may be seen that, excluding the few cases

TABLE 1.—MORTALITY IN DIFFERENT FORMS OF β HEMOLYTIC STREPTOCOCCAL INFECTIONS WITH BACTEREMIA.

	No.	Death.	Mortality, %.
Endocarditis	5	5	100.0
Scarlatina	3	3	100.0
Erysipelas and cellulitis	28	24	85.7
Abscesses and wound infections	43	35	81.4
Primary focus obscure	39	31	79.5
Tonsillitis and respiratory infection	15	9	60.0
Puerperal sepsis	5	3	60.0
Mastoiditis	28	15	53.6
Total	166	125	75.3

of scarlatina and endocarditis, the highest mortality rate (85.7%) occurred in erysipelas and cellulitis, and the lowest (53.5%) in mastoiditis. These figures are again very close to those published by Keefer and his associates. The number of cases of puerperal

* I am indebted to Drs. Dean Lewis, Samuel Crowe, and Nicholson Eastman for permission to include cases occurring on the surgical and obstetrical services.

sepsis is so small that our figures are probably not trustworthy. Colebrook and Purdie[13] give an average mortality rate of 71% for 82 cases, observed during 4 years from 1932 to 1935.

The mortality rate in all infections due to hemolytic streptococci will be influenced not only by the form of infection, but by the age of the patient, his previous physical condition, and the presence of such chronic diseases as diabetes. We need not enter into a discussion of these factors, however, since Keefer, Ingelfinger, and Spink have considered them in detail.

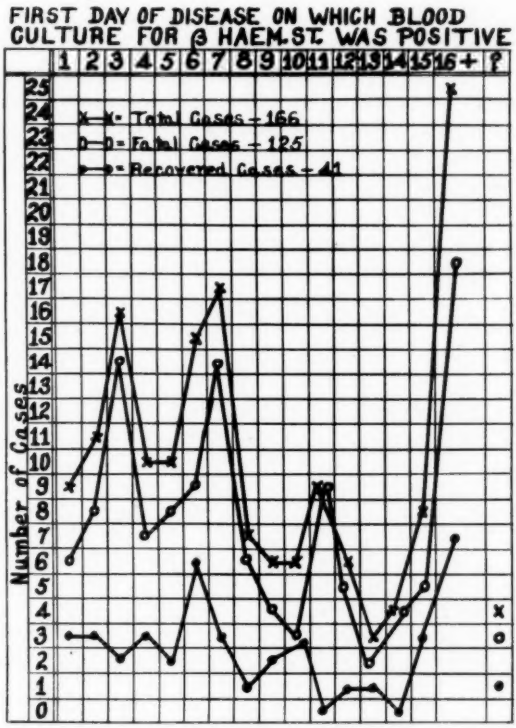
FIRST DAY OF DISEASE ON WHICH BLOOD CULTURE FOR β HAEM. ST. WAS POSITIVE
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16+ ?
X—X = Total Cases = 166
O—O = Fatal Cases = 125
•—• = Recovered Cases = 41
Number of Cases
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25

CHART 1.—Day of appearance of positive blood culture in streptococcemias.

We have been interested to gain some information concerning the day of disease upon which invasion of the blood first takes place. Although it would require daily blood cultures from the moment of onset of the infection to obtain accurate figures, still Chart 1 has some slight value, for repeated blood cultures were made on 2 to 10 occasions from 78 of the patients, 26 times in those that recovered, and 52 times in those that died, and in 24 patients positive cultures were preceded by negative cultures.

The chart shows two periods in which an invasion of the blood

was most frequently demonstrated, first during the first week of the disease, 88 cases, and second after the fifteenth day of disease, 16 cases. The fatal cases appear to be almost entirely responsible for these peaks. The early deaths occurred in the patients with acute fulminating infections, the later deaths represent, in general, terminal invasions of the blood.

In the fatal cases, the number of colonies of hemolytic streptococci in the blood varied from less than one colony per cc. to myriads. In 3 instances the blood cultures became negative before death. In the non-fatal cases, the numbers of colonies per cc. varied from less than 1 colony per cc. to 125 colonies per cc. in 1 case of mastoiditis. In 7 other patients the number of colonies per cc. varied from 25 to 80 on at least one occasion. The septicemia in 4 of these 7 cases followed mastoiditis. In 10 of the 26 cases that recovered, more than 1 positive blood culture was obtained. In 1 case of mastoiditis 6 out of 10 cultures proved positive, and in 1 case of tonsillitis 4 out of 6 blood cultures showed a growth of hemolytic streptococci.

The duration of the disease in the 125 fatal cases was as a rule short, varying from 2 to 105 days, but averaged only 12.5 days (Table 2). In 103 (82.4%) of these cases the disease lasted less than

Table 2.—Average Duration of Infections in Days.

	Recovered.		Fatal.		
	No.	Duration.	No.	Duration.	Total.
Scarlatina	..	...	3	12.5	3
Erysipelas and cellulitis	4	22.0	24	9.1	28
No primary focus	8	56.6	31	14.2	39
Abscess and postoperative	8	53.85	35	9.8	43
Respiratory infections	6	24.0	9	13.6	15
Puerperal sepsis	2	77.0	3	9.5	5
Mastoiditis	13	44.5	15	19.8	28
Total	41		120		161

Table 3.—Duration of Disease.

	Weeks.															
	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	Total.
Recovered	3	3	6	1	3	6	5	1	2	2	3	1	2	1	1	40
Fatal	42	40	21	7	6	1	2	1	3	..	1	..	..	..	1	125

3 weeks, and in 42 (or over one-third) the patient died within 1 week after onset (Table 3). In the non-fatal cases, the disease was prolonged, frequently being complicated by metastatic foci of infection and sometimes by relapses with reinvasion of the blood. In 41 patients the average duration of disease was 45.5 days; the shortest period of illness being 4 days, the longest being 6½ months.

The cases of mastoiditis, otitis media, and sinusitis showed the greatest number and variety of complications, for they occurred in 30 (93.7%) of all 32 cases. The patients with erysipelas and cellulitis developed the smallest number of complications, for these occurred in only 13 (44.3%) of all 28 cases. It is well to recall the fact

that the mortality was highest in the patients with erysipelas and cellulitis and lowest in those with mastoiditis.

Even more dangerous to the life of the patient than an invasion of the blood stream by hemolytic streptococci is an extension of the infection to the peritoneal cavity or to the meninges. Peritonitis occurs most commonly as a complication of puerperal sepsis, while meningitis is the dreaded sequel to mastoiditis and sinusitis.

Recovery from streptococcal peritonitis rarely occurs. All of Keefer's 7 cases died.

Recovery from streptococcal meningitis is perhaps still less common. Few proven cases of the disease, before the use of prontosil or sulphanilamide, are known to have survived. Gray[29] has stated that streptococcal meningitis is fatal in 97% of cases; Anderson[1] collected from the literature 66 cases that had recovered. Trachsler and his associates[69] have found 110 recoveries recorded, but state that only 2 of 71 cases that they had observed previous to the use of prontosil and sulphanilamide had survived the infection. Neal and Appelbaum[49] state that among 274 cases of streptococcal meningitis only 15 recovered, and but 9 of these were due to β hemolytic streptococci. From these figures, one would be justified in concluding that at the very most 5% to 10% of cases of meningitis due probably to all forms of streptococci recover, and that the mortality in β hemolytic streptococcal infections approaches or exceeds 95%.

Sulphanilamide. Now that we have established some standard by which we may estimate the value of any therapeutic measure employed for most serious forms of hemolytic streptococcal infection, namely those associated with septicemia, meningitis, and peritonitis, we may discuss the results that have been obtained by the most recent therapeutic procedures.

Among the numerous chemical compounds and soluble dyes that have been employed in an effort to find one that would prove to be effective against the hemolytic streptococcus, there is only a single group that deserves consideration, but this group warrants all of our attention.

For a year or two before Domagk's[17a,b] communication in 1935, a chemical called "Prontosil" or "Streptozon" had been used in Germany for the treatment of various infections. Levaditi and Vaisman[39] as well as Domagk were actively engaged at this time in studying the experimental effects of the drug in mice. But the original chemical substance, the hydrochloride of 4 sulphamido 2′, 4′ diamino 3—benzene, known as "prontosil," was soon replaced by the disodium salt of 4 sulphamido-phenyl-2′-azo-7′-acetyl amino-l′-hydrooxynapthalene-3′, 6′ disulphonic acid, a more readily soluble compound known as "Prontosil soluble." At about this time Tréfouël, Tréfouël, Nitti, and Bovet,[70] working in the laboratory Fourneau in Paris, showed that para-aminobenzene sulphona-

mide, now known as sulphanilamide, was highly effective in its curative action upon mice infected with hemolytic streptococci.

It would hardly be profitable to discuss in detail the chemical structure of these compounds, or to do more than allude to the fact that numerous allied substances are constantly being synthesized and tested, in the hope that a drug may be found which possesses advantages over sulphanilamide, or that is active against other bacteria. But one cannot leave this subject without at least mention of the chemical, sodium sulphanilyl sulphanilate, which Dochez[16] has recently found to have a remarkably beneficial effect in distemper, a disease due not to bacteria but to a filterable virus.

We will, therefore, confine our attention to the properties of para-aminobenzene sulphonamide, or sulphanilamide, and consider exclusively its therapeutic effects upon infections due to hemolytic streptococci, even though it is now known to be of value in the treatment of infections due to meningococci and gonococci, to be curative in some instances of pneumococcus meningitis or in other infections due to pneumococcus Type III, and to modify, as Rich and Follis[57] have shown, the development of experimental tuberculosis in the guinea pig.

During 1935 many brief clinical reports appeared both in the German and French literature, indicating that the drug was of value in the treatment of streptococcal infections, but it was not until the careful clinical and experimental work of Buttle, Gray, and Stephenson[9] and of Colebrook, Buttle, and O'Meara[14] stimulated the work of Long and Bliss that the drug became at all familiar in this country.

The pharmacologic action of the chemical has been studied experimentally, particularly by Marshall, Emerson, and Cutting.[42,43a,b,44a,b] They find that it is absorbed quite as rapidly from the gastrointestinal tract as from the subcutaneous tissues, and since it is not highly soluble, oral administration is desirable when this is possible. It has been suggested by Long and Bliss[40b,c] that an average daily dose of 1 gm. by mouth per 20 pounds of body weight is theoretically desirable, but in practice, it is often useful to administer somewhat larger doses to adults for a few days. A daily dose of 6 to 9 gm. for 2 to 3 days may be advisable in exceptionally severe infections, and Colebrook and Purdie[13] have employed, under these circumstances, as much as 12 to 15 gm. a day. The optimum dose is usually best arrived at in the individual case by determining the blood concentration, which according to Long and Bliss should reach a level of approximately 10 mg. %. The drug may be given, however, by the subcutaneous route or intrathecally when this seems necessary. It is soluble in the proportions of 8 gm. to 1000 cc. of water. An accurate quantitative method for the determination of the chemical in solution has been described by Marshall and his associates,[43a] so that it is a comparatively simple matter to

determine its concentration in the blood, urine, body fluids, and tissues. The chemical can be detected in the blood within an hour after it has been administered either orally or subcutaneously and within 3 or 4 hours reaches its maximum concentration in the serum. Within a few (3 to 4) hours after ingestion it appears in the urine and continues to be excreted for 24 to 48 hours. In the dog, the substance appears to be excreted unchanged in the urine; while in the rabbit, cat, and man, varying amounts of the chemical appear as an acetyl derivative, which is practically inactive therapeutically.[43b] The acetylated product forms a comparatively large proportion of the material that is excreted in the rabbit. The chemical is readily diffusible and is found in the spinal fluid and pleural exudates of man in concentrations only slightly lower than those in the blood. Indeed Marshall and his associates have found that it permeates most of the organs of the body, so that concentrations comparable to those in the blood can be found in the skeletal muscles, heart, skin, and viscera. The lowest figures were obtained for fat and bone. The diffusibility of the chemical appears to account for the fact that the sulphanilamide clearance in the dog amounts to only 20 to 30% of the creatinin clearance determined simultaneously. A large part of the sulphanilamide, presumably filtered through the glomeruli, is reabsorbed by the tubular epithelium. It was found by Marshall in some cases of nephritis that the excretion of the drug was considerably delayed and as this proves to be of fairly constant occurrence, equivalent doses of the drug result in higher concentration in the blood of nephritics than in patients with normal kidneys. It is important that the drug should be administered in sufficient quantities and at the proper intervals to maintain as constant and as nearly optimal concentration in the circulating blood as possible. As the drug is rapidly excreted in the urine, Marshall has suggested that the chemical be administered at least every 4 hours. When one follows this method it has been found that it requires from 2 to 3 days to establish an equilibrium between the amount ingested and the amount excreted, and thus to maintain the concentration of the drug in the blood at a level of at least 10 mg. %. This is the concentration which Long and Bliss[40b,c] have estimated to be desirable or even essential in order that the drug should be most effective.

It is, naturally, of the greatest importance that we should understand the manner in which the drug produces its effect. It is known that neither "Prontosil" nor "Prontosil soluble"[12] has the slightest injurious action upon hemolytic streptococci *in vitro*. It is now recognized, however, that these drugs probably owe their therapeutic action to the fact that they are converted into sulphanilamide in the body (Long and Bliss, Fuller).[25,40e] Unlike prontosil, sulphanilamide itself, as has been shown by Buttle,[9] Colebrook,[14] Long and Bliss,[40d] and Fischer,[20] exerts a definite and measurable effect upon the growth

of hemolytic streptococci *in vitro*. This can best be demonstrated by employing cultures of hemolytic streptococci which contain very small numbers of organisms per cubic centimeter. Under these circumstances the chemical possesses a definite bacteriostatic effect, suppressing the multiplication of the bacteria. It does not, however, in the concentrations used, destroy the hemolytic streptococci, as subsequent growth is always observed.

Although one can probably determine the activity of sulphanilamide against any variety of bacteria by this procedure, a more satisfactory method is to measure the therapeutic properties of the drug against infections produced experimentally in animals.

Studies instituted to examine the mechanism by which sulphanilamide acts in the body indicate that it acquires no further virtue than that which can be demonstrated in the test tube. Levaditi and Vaisman[39] suggested that the chemical rendered hemolytic streptococci more susceptible to phagocytosis in the peritoneum of the mouse by injuring or destroying their capsules and neutralizing the leukocidin, but Bürgers[8] could not confirm the observation, and the work of Long and Bliss[40d] and of Gay and Clark,[26] seems to have established the fact that the drug simply retards the growth of hemolytic streptococci in the peritoneum of the mouse or in the pleural cavity of rabbits, and that it has *in vivo* no other demonstrable property than that which it possesses *in vitro*, namely one of bacteriostasis. Phagocytosis appears to be the only demonstrable means that the body has to dispense with the infecting organism. This is carried on in the mouse by the polymophonuclear leukocyte, though Domagk[17c] has shown that macrophages are also active during the early stages of the process. McKinney and Mellon[41] conclude from their experiments that the phagocytic response depends upon the type of organism, some strains calling forth neutrophils, others implicating the macrophages. That neutrophils, nevertheless, are essential to the protective mechanism of the mouse is definitely indicated by the experiments of Long and Bliss,[43d] who showed that treatment by sulphanilamide became completely ineffective in mice made leukopenic by injections of benzene. In the rabbit, according to Gay and Clark,[26] protection depends upon active phagocytosis by the macrocyte. It must be noted, on the other hand, that Mellon, Gross, and Cooper,[45] experimenting with strains of hemolytic streptococci of varying virulence, could not convince themselves that phagocytosis was responsible for the therapeutic effect of either sulphanilamide or of "prontosil" in infections of mice or of guinea pigs, while Osgood,[51] working with cultures of human marrow, concludes that the value of these drugs rests upon their ability to neutralize toxins.

Since it has been possible, through experimental and clinical studies to establish some of the conditions under which therapeutic action of sulphanilamide is most effective, we must conclude that

there are at least two which are essential. The first is that the infecting organism should be subjected to a concentration of the chemical sufficient to produce an optimal bacteriostasis; and the second, that the body should acquire and retain the power to rid itself of comparatively small numbers of viable and perhaps highly virulent organisms. One method, by which this seems to be effected in experimental animals, is through phagocytosis.

The clinical results which have followed the use of sulphanilamide tend to bear out some of these assumptions, but the literature is literally flooded by reports of such short series of cases, and the drug is being employed so widely for such diverse and such indefinite types of infection, that it will require prolonged and critical study to determine not only the conditions in which it is undoubtedly of immense value, but to define in addition the limits of its usefulness, as well as to recognize the dangers incidental to its employment.

The drug seems to be effective in infections due to several, and possibly all, types of hemolytic streptococci belonging to the Lancefield Group A,[13] and in infections of animals caused by some but not all strains of Group C (Lancefield).[62] Long and Bliss[40f] have found the drug inactive in urinary infections due to hemolytic streptococci belonging to Group D (Lancefield), while Colebrook and Purdie[13] have not observed that it has any effect upon puerperal infections caused by anerobic streptococci.

There is not, at the present time, sufficiently accurate information at hand to discuss the action of sulphanilamide upon all forms of infection due to hemolytic streptococci, and I will, therefore, confine the discussion to a consideration of its therapeutic effects in a few of the more serious forms of streptococcal infection.

One of the severest tests to which the efficiency of this drug could be put is in the treatment of meningitis due to hemolytic streptococci, for as we have seen at least 90 to 95% of these patients die. The therapeutic results in this type of infection have been nothing short of brilliant. During the last few months recoveries have been reported in at least 39 patients who were treated with prontonsil or sulphanilamide or a combination of the two drugs. Undoubtedly the recoveries at the present time far exceed this number. Trachsler and his associates[69] have recorded 4 recoveries out of 7 cases, Long and Bliss[40b,c] 2 out of 4, Schwenke and his associates[61] 3 out of 4, and Neal and Appelbaum[49] 13 recoveries out of 17 cases.

Most of these recoveries have occurred in patients suffering from streptococcal meningitis secondary to mastoiditis, and it is important to pay some attention to the combination of circumstances under which the drug was often used. In a large proportion of cases the primary focus of infection was drained surgically; in many, the drug, in the comparatively high concentration of 0.8%, was brought in direct contact with the infected meninges by intrathecal injections, and in all the infected meninges have been drained re-

peatedly by lumbar puncture. It seems reasonable to suppose that these accessory procedures were of some benefit, for it cannot be sufficiently emphasized that, as far as we know at the present time, the actual cure of the infection and elimination of the hemolytic streptococcus depends in the last analysis, not upon the drug, but upon the protective forces of the body. These are brought to bear upon an invading organism, made particularly vulnerable in some way by the action of the drug. Colebrook and Purdie[13] have shown

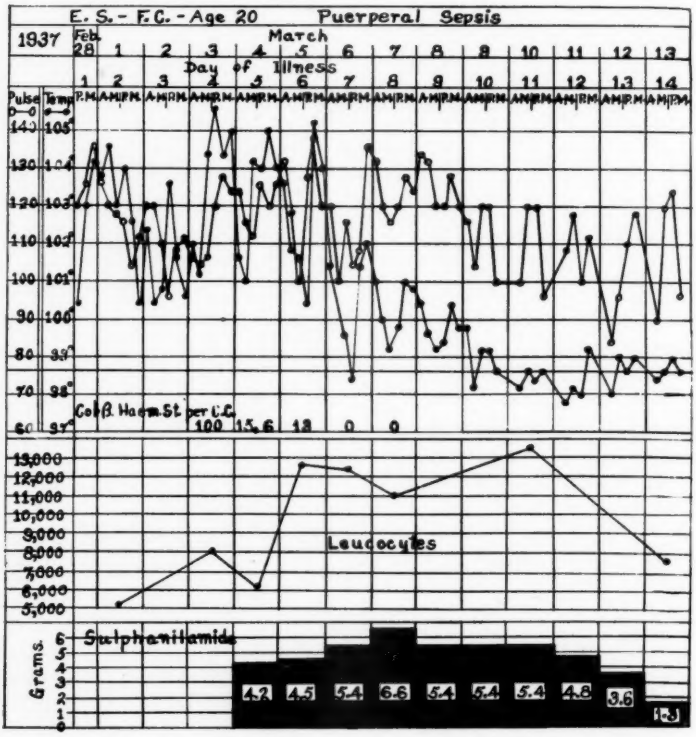

CHART 2.—A case of puerperal sepsis treated with sulphanilamide.

for instance, that the whole blood of patients suffering from streptococcal infections who have been treated with sulphanilamide becomes highly bactericidal for hemolytic streptococci, though it is known that the drug does not impair the virulence of viable organisms.

It is possible that some of these accessory factors are absent in the patients with streptococcal peritonitis which have been treated with sulphanilamide, for failures have been recorded in several instances.[10,40g] On the other hand, recoveries have been observed, and Dr. Edwards Park has allowed me to mention a case of peri-

tonitis in a premature colored infant who 1 month after birth developed otitis media and peritonitis, due to β hemolytic streptococci. He recovered after repeated subcutaneous injections and 1 intraperitoneal injection of a solution of sulphanilamide combined with $\frac{M}{6}$ sodium lactate, in spite of the fact that repeated transfusions were necessary to combat a severe hemolytic anemia, produced apparently by the sulphanilamide. Colebrook and Purdie[13] report 2 recoveries out of 4 cases of peritonitis occurring in women with puerperal sepsis.

Indeed, the treatment of puerperal sepsis has been attended with highly satisfactory results. Colebrook and his associates[11–12], Foulis and Barr[22] and Gibberd[27] among others, have shown a very pronounced reduction in the mortality from puerperal infection due to β hemolytic streptococci with the introduction of prontosil and sulphanilamide. The results of Colebrook and Purdie[13] are particularly striking on account of their conservative attitude. The death rate for cases with positive blood cultures with or without peritonitis was reduced from a previous average of 71% to 27.3% in 22 cases treated with these drugs.

Chart 2 shows the essential features in a patient suffering from puerperal sepsis with positive blood cultures, who recovered after treatment at this hospital.

A colored woman of 20 was admitted to the obstetrical service of this hospital (Unit 100717) on March 1, 1937, having been delivered outside the hospital 6 days previously. Three days after delivery she had a "slight cold," and on the day of admission the lochia increased, she felt badly and had slight fever. She was found on admission to have a temperature of 103°, a red pharynx, and râles at the bases of the lungs. She appeared very ill. The blood pressure was 118/84; the leukocyte count 5200. The urine showed no albumin. A blood culture on March 3 showed 100 colonies of β hemolytic streptococci per cc. and she was transferred to the medical wards.*

The significant features of her illness are the early invasion of the blood, the rapid decrease in the numbers of colonies per cc. with a subsequent steady rise during the first days of sulphanilamide therapy, followed by a rapid disappearance of hemolytic streptococci from the blood, a fall in temperature, with a rise in leukocytes, and rapid recovery without complications.

Erysipelas is a disease which furnishes signs of advance or regression that are more or less readily measurable. One gains the impression possibly on this account that it is a form of streptococcal infection, which is very favorably influenced by the action of sulphanilamide. The literature contains accounts of hundreds of cases which have been treated, with few fatalities. It is usually stated that the

* This case has been included by Drs. Long and Bliss in their statistics.[10,40g]

spread of the infection is prevented and that the duration of the disease is shortened, the temperature falling within 24 to 48 hours after treatment is started.[54] Hageman and Blake[31b] give a duration for control cases of 13.9 days; for treated cases 5.3 days. Snodgrass and Anderson,[63] who report the results of treatment in 160 cases, state that the mortality was reduced from 9.6% in a control series of 312 cases to 2.5% for the cases treated with prontosil and sul-

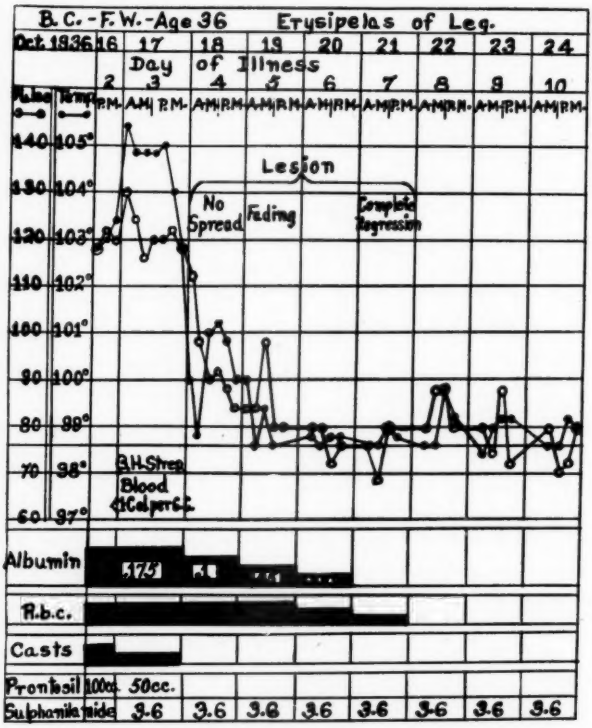

CHART 3.—A case of erysipelas treated with sulphanilamide.

phanilamide. Hageman and Blake include in their series 2 cases of erysipelas in infants, showing positive blood culture, with recovery. The results in these 2 patients are particularly striking, for under such conditions, the disease is almost always fatal in infants.

Chart 3 illustrates the course of a rapidly spreading erysipelas treated with sulphanilamide.

A white woman of 36 years was admitted to the medical service of this hospital on October 16, 1936, complaining of a painful swelling of the leg. She had had an ulcer of the leg for 10 weeks. The night before admission, she had had a chill, fever, and a red, tender, painful swelling had appeared about the ulcer.

The small ulcer was about the size of a dime, surrounded by a fiery red, tender swelling. A brawny swelling showing red indurated areas and sharply defined margins extended from the ankle almost to the knee. The blood pressure was 110/70; the patient appeared very ill; leukocytes 12,000 (Chart 3).*

The significant features are the disappearance of hemolytic streptococci from the blood, the cessation of spread, the critical fall in temperature on the fourth day of disease, and the rapid recovery without complications under sulphanilamide therapy.

The conditions on admission were those that one usually associates with a rapid and very unfavorable progress. It will be remembered that in our control series 85% of such cases terminated fatally.

Scarlet fever presents clinical and immunologic problems (Francis[23]) that differ materially from those in erysipelas, and I have gained the impression that sulphanilamide has comparatively little, if any, influence upon the course of the acute illness. Hageman and Blake[31b] conclude from an analysis of 7 cases that the drug shows no effect in the toxic stage of the disease, though none of their patients developed complications. Peters and Havard[54] gained the impression that the number of complications was reduced in their treated cases. Possibly with further experience it may be possible to employ sulphanilamide more effectively in this disease, but from what we now know about the action of the drug, it is unlikely that the toxemia itself would be affected. One might, nevertheless, hope to obtain some relief of the local infection of the throat and thereby prevent the distressing and serious complications that so frequently follow scarlatina.

In our limited experience, however, it has proved difficult to rid the throat and tonsils of hemolytic streptococci by the use of sulphanilamide.

It has already been pointed out that recovery from a local streptococcal infection may take place without elimination of the organism from the point of infection. Colebrook and Purdie[13] found this to be true in puerperal infections of the uterus, and it is well known that after an attack of acute tonsillitis, hemolytic streptococci may remain in the tonsils for weeks or months.

In an attempt to hasten recovery from acute infections of the tonsils and throat by hemolytic streptococci in patients suffering from acute hemorrhagic nephritis, we have used sulphanilamide in 15 cases in moderate sized doses for fairly long periods of time. Cultures from the throat of all of these patients, before treatment was begun, showed moderate to great numbers of β hemolytic streptococci (Table 4). Cultures were made repeatedly during the course of treatment and from the interior of the tonsils from 13 of these patients who after treatment were subjected to tonsillectomy.

* The case was included in the statistics published by Drs. Long and Bliss.[10,40g]

The tonsils from 6 of these patients, who had received from 18 to 66 gm. of sulphanilamide over periods of from 6 to 25 days, and whose blood sulphanilamide varied from a concentration of 7 to 19 mg. %, showed a heavy growth of hemolytic streptococci, while in one other patient who had tonsillitis and sinusitis and who had received 39 gm. of sulphanilamide over a period of 12 days, cultures from the throat were almost continuously positive for 6 months. Four of these patients manifested mild symptoms of intoxication such as slight fever, headache, nausea, and cyanosis.

TABLE 4.—EFFECT OF SULPHANILAMIDE UPON LATENT INFECTION OF TONSILS BY HEMOLYTIC STREPTOCOCCUS.

No.	Original culture.	Sulphanilamide.			Subsequent throat cultures.		Culture from tonsils at operation.	Toxic symptoms.
		Total grams.	Days admin.	Blood concent., mg. %.	+.	0.		
1	++++	18.0	6	....	1	1	No tonsillectomy	0
2	++++	58.2	6	6.4–7.7	3	3	++++ (pure cult.)	0
3	++++	42.9	17	7.0–19.8	2	2	++++ (pure cult.)	0
4	++	28.8	25	7.2	8	..	++++ (pure cult.)	0
5	+++	81.0	24	....	..	3	0	0
6	++	66.0	12	....	2	..	++++ 90%	+
7	++	39.0	12	....	3	..	No tonsillectomy	±
8	+++ (antrum inf.)	58.8	32	6.5–10.0	5	3	No tonsillectomy cults. from pharynx pos. for 6 months	0
9	++++	18.6	7	6.0–7.6	4	1	0	+
10	++	27.9	12	6.9–11.0	1	6	0	+
11	++	43.2	12	10.2–16.4	3	4	0	++
12	++++	20.7	4	9.7–10.0	1	2	No tonsillectomy	+++
13	+	45.0	9	....	..	4	0	0
14	+++	16.2	6	....	1	3	0	+
15	++++	19.0	5	....	2	3	++++	++

Six patients whose tonsils did not show hemolytic streptococci at operation, and 2 whose throat cultures became negative received from 16.2 to 81.0 gm. of sulphanilamide over periods of from 6 to 32 days, during which time the concentration of sulphanilamide in the blood varied from 6 to 16.4 mg. %. Six of these 8 patients had mild symptoms of intoxication.

It seems clear to us that the administration of even comparatively large amounts of sulphanilamide over considerable periods of time will not always eliminate hemolytic streptococci from persistent and latent infections of the tonsils. Swift, Moen, and Hirst[66] have had the same experience in their study upon tonsillitis in rheumatic patients, while Colebrook and Purdie[13] report that hemolytic streptococci were recovered from cervical swabs taken on discharge from the hospital in 39 of 81 (48%) of their cases of puerperal infection that had recovered under sulphanilamide, and that 6 of 35 patients (17%) still showed positive culture for hemolytic strepto-

cocci 3 to 6 weeks later. Indeed, this is found to occur even in experimental infections, for Levaditi and Vaisman[39] and Long and Bliss,[40b,c] as well as Colebrook and his associates,[12,13] have reported the persistence of latent foci of hemolytic streptococci in mice treated for long periods by sulphanilamide.

The difficulty of eradicating hemolytic streptococci completely from the focus or foci of infection may very well explain the recurrences and relapses that have been occasionally encountered in some patients after cessation of treatment by sulphanilamide. Unless the protective mechanism of the body is capable of resisting an exacerbation of the infection, a renewed invasion of tissues by hemolytic streptococci is likely to occur.

It is for reasons such as these that the surgical methods commonly employed in the treatment of infections should not be abandoned when sulphanilamide is employed. Free drainage of infected areas is undoubtedly beneficial, and all possible means should be used to assist the body to combat the invasion of organisms, the multiplication of which appears, from studies made up to the present time, simply to be suppressed by the action of sulphanilamide.

Sulphanilamide, first thought to be almost innocuous, is now known to produce at times a variety of unpleasant symptoms, and is for a few patients highly toxic. Little information can be gained concerning this phase of the subject from animal experimentation; for, except in enormous doses, it is almost harmless for laboratory animals (Raiziss,[55] Hawking[34]). Marshall, Cutting, and Emerson[43c] find that when the drug is administered orally it requires 3.8 gm. per kg. to kill 50% of mice, and that dogs have recovered from doses of 2 gm. per kg. This would be equivalent to a dose of at least $\frac{1}{4}$ of a pound of the drug in a person weighing 150 pounds. The dogs, however, that received the large doses, were salivated, vomited, had diarrhea, hyperpnea, excitement, muscular weakness, ataxia, and presented signs of stimulation and depression of the central nervous system leading to a condition of spastic rigidity of the limbs and hyperesthesia. All but one of 9 dogs recovered within 12 to 24 hours. Prolonged administration of sublethal doses did not produce any evidence of chronic intoxication in rats or dogs. The acetyl derivative to which the drug is partially changed in many animals appears to be more toxic than the original substance.

In man, on the other hand, a long series of toxic effects have been described.[10,31a,b,40b,c,g] The subject is of great importance though it is only possible to allude to it at this time. It is quite impossible to predict what toxic symptoms will become manifest in any particular patient. Some patients have taken 1.2 to 2.4 gm. of the drug daily for months without the slightest ill effects. Nevertheless, in a fair proportion of patients receiving larger doses of the drug there is cyanosis. Many patients experience malaise, anorexia, dizziness, somnolence, nausea, headache, and are depressed. Vomiting is not

uncommon. These are symptoms which have been observed in animals intoxicated by the drug and are dependent, no doubt, upon a direct action of the chemical. Febrile reactions, with or without skin eruptions are frequently encountered and are difficult to interpret, for one may be puzzled to know whether the fever is due to the drug, to an exacerbation of the infection, or to the occurrence of a complication. Morbilliform, and erythematous eruptions have been described, occasionally progressing to a dermatitis exfoliativa.[19,24,28,31a,47,48,59] They may be precipitated by exposure to light.[50] One patient is described as having a violent attack of urticaria accompanied by difficult breathing which appeared after the first few doses of the drug.[58] Optic neuritis has been recorded.[7] The acute anemias with evidence of hemolysis are particularly alarming;[33,37] but when the drug is stopped and transfusions are given, recovery is extraordinarily prompt. The instances of agranulocytosis are more serious and deaths are reported as a result of this complication.[3,5,35,60,73]

Southworth[64] showed some time ago that the CO_2 combining power of the blood was almost regularly lowered and Marshall, Cutting, and Emerson[43c] have demonstrated experimentally that this is due to an acidosis associated with a disturbance in the acid base equilibrium. On this account sodium bicarbonate is administered regularly with sulphanilamide. The cause of the cyanosis is somewhat obscure. It may be associated with moderate degrees of hemoglobinemia or sulphemoglobinemia, but this does not appear to be sufficient to explain entirely the intensity of the bluish color that develops in many of these patients.[2,13,15,39,52]

Although the drug is excreted in the urine in considerable concentration, it does not appear to injure the kidneys.

In some patients, symptoms may appear after the first few doses of the drug. In other patients, they do not arise until the drug has been administered in full doses for several days. This is usually true of the "drug fever," which Blake[31a] pointed out was most likely to make its appearance between the seventh and tenth days after sulphanilamide had been started. Though a number of the toxic manifestations are to be attributed, as Marshall[43c] suggests, directly to the drug, others such as asthma, the acute anemia, and the agranulocytosis are so rare that they should be ascribed to a peculiar idiosyncrasy of the particular patient.

Most of the unpleasant symptoms, and especially those referable to disturbances of the nervous system, subside promptly when the drug is stopped and large amounts of fluid are administered. Under these circumstances, the fever usually returns to normal within 36 to 48 hours. The eruptions may persist for some days.

It seems obvious that when the drug is used for a specific purpose in a severely ill patient, it may have a remarkably beneficial effect and has undoubtedly saved many lives, but when it is used indis-

criminately for minor ailments, it may prove ineffective, produce unpleasant symptoms and, in rare instances, be actually dangerous.

Conclusions. Hemolytic streptococcal infections, in which there is an invasion of the blood, the meninges, or the peritoneal cavity, are fatal in a large proportion of patients. The mortality in blood stream infections due to hemolytic streptococcal infections varied in 166 patients from 53.6% in mastoiditis and otitis media to 85.7% in erysipelas and cellulitis, while at least 95% of cases with meningitis succumb, and the mortality in peritonitis is perhaps still higher. Some factors contributing to this high mortality have been commented upon.

The pharmacologic and experimental action of sulphanilamide has been discussed, and the remarkable therapeutic effect of this drug in the serious infections due to hemolytic streptococci has been recorded. Attention has been drawn to the fact that it has a most pronounced effect in the early stages of these infections, but that it may fail to sterilize foci of latent infection in the tonsils. Some of the evidences of intoxication have been recounted, and it is pointed out that the most alarming of these are rare and probably depend upon an individual idiosyncrasy to the drug.

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STUDIES IN DIABETES MELLITUS.

VI. Mortality and Longevity of Diabetics.

By Elliott P. Joslin, M.D.,

Medical Director of the George F. Baker Clinic, New England Deaconess Hospital, Boston, Mass.,

Louis I. Dublin, Ph.D.,

Third Vice-President and Statistician, Metropolitan Life Insurance Company, New York City,

and

Herbert H. Marks,

Metropolitan Life Insurance Company, New York City.

The average length of life of diabetics has definitely increased in recent decades, particularly since the discovery of insulin. It is apparently still increasing. Reliable measures of this improvement, however, have been lacking. Until now the only method available has been to compare the average duration of the disease from onset to death among diabetics in successive calendar periods. This method is not statistically correct, but as long as the conditions of

treatment and the mortality rate of diabetics were fairly stable, the result served as an approximation of the truth. But, when an important influence such as insulin came into being, the balance was upset, and the average duration of diabetes in fatal cases of recent years is no longer an accurate measure of the longevity of the diabetic. Indeed, such data on fatal cases alone may even mislead because they probably include an undue proportion of patients who were neglected or poorly treated, or who died of accidents or acute emergencies.

There are several other objections to the use of the average duration of the disease in fatal cases as a measure of longevity today: 1, In a group of diabetics under the care of any one physician or clinic, some of the patients were originally diagnosed elsewhere. These cases are the survivors of larger initial contingents of patients of other physicians. The longevity of the other patients of these physicians is unknown. The patients diagnosed elsewhere, therefore, have previous histories of diabetes of varying durations, many of them quite long. These cases artificially increase the average duration of the whole group. 2, The date of onset of diabetes is often not exactly determinable, and this may tend to increase or decrease the recorded duration of life of patients. 3, Cases with sudden onset and short duration of life are often not diagnosed and, therefore, do not get into the experience. This applies also to cases with somewhat longer durations, which because of lack of clear-cut symptoms of the disease are not recognized as diabetes. Somewhat different are certain other objections of a statistical nature. 4, When the data are classified by calendar year periods, deaths with longer durations are necessarily classified in the later periods and, consequently, boost the averages in those periods. 5, With a rapidly growing number of patients, even though the proportion of deaths to total cases may decrease, the actual numbers may go up. In this instance, the average duration of the fatal cases is relatively short, particularly so if there is a high selective death rate in the early years of the disease.

These defects in the method of average duration are clearly not all in one direction. They tend to counterbalance each other, but there is no way of telling how far this goes. In any event, there is an indefinite period of time, in the data based on duration from onset to death, in which no deaths can be recorded, because relatively few cases are diagnosed at the very onset of the disease. This is a serious matter in a mortality experience.

These many difficulties disappear only when the actual period of observation on each patient is recorded, and the longevity of the group is measured as for a population, or, more strictly speaking, when a survivorship experience of the type common in insurance work is computed. The fundamental unit is the year of life lived. This method permits the computation of death rates per head *per*

annum at specific ages. Age is, of course, a vital factor in mortality. One can make comparable tabulations for as many groups as is warranted by the size of the group studied, as, for example, by sex, residence, occupation, and so forth. Details of this method of mortality analysis are not given here, but may be found in any of the standard textbooks dealing with the construction of mortality tables.* One special requirement in tabulating the data for a group of patients is that the follow-up must be practically complete. In the present instance of Dr. Joslin's patients, the follow-up has been carried out as fully as practicable and the number of "lost" or untraced cases in the group as a whole is less than 1% and in the special groups seldom, if ever, over 2%.

The present paper covers the total experience on all true diabetics treated by the senior author and his associates who were first treated in and discharged from the hospital during 1897 to 1928, or first seen at the office or in consultation during those years. These patients were traced to the anniversary in 1929 of their first hospital discharge or non-hospital observation, or to their prior death except for pre-insulin cases surviving into the insulin period who have been traced to August 7, 1929, the anniversary of the date in 1922 on which the use of insulin was begun in the Baker Clinic. Desirable as it would be to have more recent data on all patients, the amount of time and labor of the medical staff of the Clinic required to trace successfully such large numbers of persons had become too great to be carried on. It was, therefore, decided sometime ago to limit follow-up efforts to special groups of patients who were of particular significance as illustrating the influence of important factors in the longevity of diabetics. Several such groups (*e. g.*, diabetic patients under age 40 at onset; diabetic physicians; and pre-insulin era patients) on whom more up-to-date information is available, will be reported in subsequent papers. The trend of the mortality of diabetics up to 1929, however, gives a sure indication that any changes since that date are changes of degree and not of kind. This will be found to be confirmed by the trends in the special groups which are next to be reported.

In the tabulation of the mortality experiences in this and later papers, untraced or "lost" cases were included up to the last date on which they were definitely known to be living. The years designated in the text and tables are "experience" or "exposure" years and not calendar years. The "experience" year includes the period from the date of the original observation in one year or the anniversary of such date to the anniversary in the following year. The tables exclude what may be called the "immediate" mortality, that is, patients admitted to the hospital or seen in consultation

* For example, Murphy, R. D., and Papps, P. C. H.: Construction of Mortality Tables from the Records of Insured Lives, Actuarial Society of America, New York, 1922.

who were dangerously ill or moribund at the time and who died in the hospital during the first period of treatment there or within 1 week of discharge or within a week of first observation. The number of these "immediate" deaths in the experience reported here was 187, as compared with 2271 later deaths up to the 1929 anniversary.

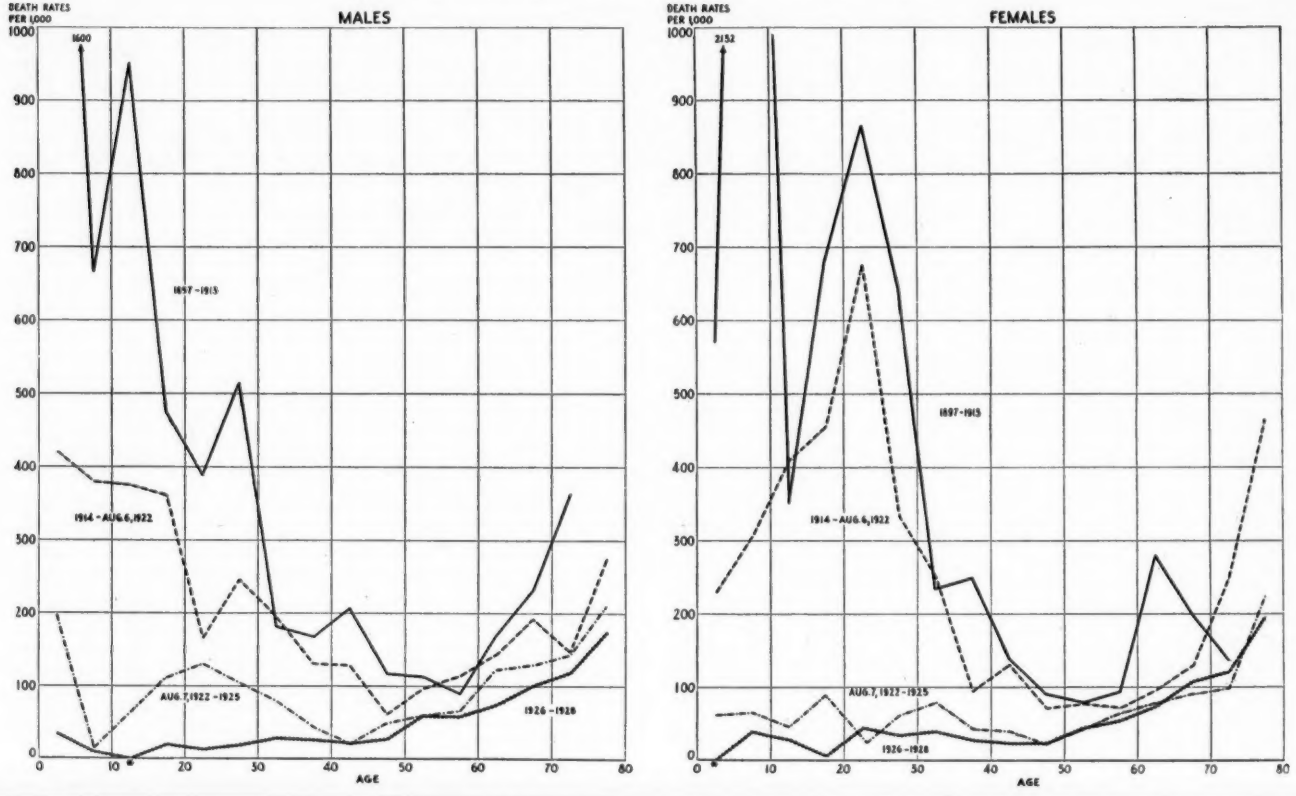
TABLE 1.—DEATH RATES PER 1000 AMONG DIABETICS IN THE NAUNYN, ALLEN AND BANTING ERAS. BY SEX AND ATTAINED AGE. EXPERIENCE OF E. P. JOSLIN, 1897 TO 1929.

Sex; age.	1897–1913.			1914 to August 6, 1922.			August 7, 1922, to 1925.			1926–1928.		
	Years of life exposed.*	Deaths.	Death rate per 1000.	Years of life exposed.*	Deaths.	Death rate per 1000.	Years of life exposed.*	Deaths.	Death rate per 1000.	Years of life exposed.*	Deaths.	Death rate per 1000.
Males.												
All ages	894	171	217.7†	3057	446	152.6†	3755	316	86.0†	4813	274	58.3†
Under 5	1	2	1600.0	12	5	422.3	15	3	196.7	28	1	35.5
5– 9	11	7	666.0	45	17	378.5	69	1	14.6	88	1	11.4
10–14	11	10	951.5	48	18	375.1	94	6	64.1	153	—	—
15–19	25	12	473.7	64	23	361.2	116	13	111.8	145	3	20.7
20–24	15	6	389.1	90	15	165.8	123	16	130.6	159	2	12.6
25–29	17	9	514.6	110	27	245.8	134	14	104.9	157	3	19.2
30–34	39	7	181.8	103	20	195.1	150	12	80.0	241	7	29.1
35–39	60	10	167.6	182	24	132.0	205	9	43.9	222	6	27.0
40–44	82	17	207.1	234	30	128.0	278	6	21.6	357	8	22.4
45–49	136	16	117.9	340	21	61.8	408	20	49.0	437	12	27.5
50–54	124	14	113.4	472	46	97.4	513	31	60.4	602	36	59.8
55–59	133	12	90.3	529	60	113.4	570	38	66.7	677	39	57.6
60–64	123	21	171.1	384	55	143.3	504	62	123.1	653	48	73.5
65–69	77	18	232.8	234	45	192.1	317	41	129.4	514	52	101.1
70–74	25	9	363.6	136	20	147.1	168	24	142.6	237	28	117.9
75–79	15	1	65.9	58	16	274.7	67	14	209.8	115	20	174.3
80 and over	1	..	...	17	4	238.8	25	6	241.6	30	8	269.6
Females.												
All ages	657	128	239.1†	2311	332	156.2†	3926	260	66.4†	5533	344	58.7†
Under 5	2	1	571.4	13	3	227.8	16	1	62.2	24	—	—
5– 9	5	11	2131.8	30	9	305.0	62	4	64.8	103	4	39.0
10–14	17	6	351.1	46	19	410.8	88	4	45.7	142	4	28.3
15–19	10	7	682.9	46	21	454.9	90	8	89.3	171	1	5.9
20–24	9	8	865.8	34	23	676.7	42	1	23.6	112	5	44.7
25–29	11	7	641.0	51	17	333.9	81	5	61.5	113	4	35.3
30–34	30	7	234.6	76	19	251.1	114	9	79.1	150	6	40.0
35–39	40	10	249.0	116	11	94.9	164	7	42.6	215	6	27.9
40–44	43	6	138.5	168	22	131.3	249	10	40.1	345	8	23.2
45–49	77	7	90.7	237	17	71.8	366	8	21.8	452	11	24.3
50–54	101	8	79.1	339	26	76.7	579	25	43.2	758	34	44.9
55–59	96	9	93.8	415	30	72.4	718	46	64.1	948	51	53.8
60–64	53	15	280.8	375	36	96.0	608	48	79.0	807	60	74.4
65–69	75	15	201.1	209	27	129.3	457	42	91.9	669	72	107.6
70–74	51	7	137.3	93	23	247.6	213	21	98.4	360	44	122.2
75–79	23	3	131.4	41	19	466.4	62	14	224.3	133	26	195.8
80 and over	13	1	75.0	25	10	405.4	16	7	441.9	32	8	252.6

* Fractional parts of years of life exposed were tabulated but the exposed in this table are taken to the nearest whole numbers.
† Standardized on basis of patient population, 1897 to 1929.

Mortality of Diabetics During Three Eras of Treatment. Table 1 gives the years of life exposed, the number of deaths and the death rates per 1,000 of the diabetics in this experience. These facts are shown in detailed attained age groups and by sex during three separate periods, namely, the Naunyn era (experience years, 1897 to

CHART 1.—Mortality among diabetics in the Naunyn, Allen and Banting Eras compared. Death rates per 1000 in specified "experience" years. By sex and age. Experience of E. P. Joslin, 1897 to 1929.



1913), the Allen era (1914 to August 6, 1922) and the Banting era (August 7, 1922, to 1928). The last is subdivided in two parts, the dividing line being the end of 1925, in order to show both the immediate effect of insulin on the death rates and the effect of the increased skill in handling it, resulting from its continued use.

TABLE 2.—PER CENT DECLINE IN DEATH RATES OF DIABETICS BETWEEN VARIOUS ERAS OF TREATMENT.* BY SEX AND AGE. EXPERIENCE OF E. P. JOSLIN, 1897 TO 1929.

Sex; age.	Per cent decline in death rates between			
	Naunyn era and second part of Banting era.	Naunyn era and Allen era.	Allen era and first part of Banting era.	First and second parts of Banting era.
Total.				
All ages	74.4	32.4	50.6	23.2
Under 10	98.3	74.6	82.5	60.4
10–19	97.8	34.6	80.3	82.7
20–29	95.4	41.6	77.0	65.4
30–39	85.4	23.1	63.3	48.2
40–49	81.7	29.9	63.9	27.7
50–59	42.0	4.1	34.4	7.8
60–69	60.9	38.4	23.2	17.3
70 and over	30.0	+17.3	34.2	9.3
Males.				
All ages	73.2	29.9	43.6	32.2
Under 20	98.3	50.1	78.8	84.2
20–39	91.6	36.5	54.4	71.0
40–59	61.0	16.8	45.4	14.1
60 and over	53.9	21.5	20.1	26.5
Females.				
All ages	75.5	34.7	57.5	11.6
Under 20	97.7	56.4	82.8	69.6
20–39	91.7	33.7	81.4	33.1
40–59	57.6	13.8	44.7	11.0
60 and over	53.3	29.0	35.1	+1.3

* Naunyn, 1897–1913. Allen, 1914–August 6, 1922. Banting, first part, August 7, 1922–1925; second part, 1926–1928.

The experience within each of these periods includes the observations on patients surviving from earlier periods and on new patients entering into the experience during the period. Chart 1 gives a graphic representation of the observed mortality by age and sex.

Striking improvement in the mortality of diabetic patients is clear from the chart. It is greatest in children, amazingly so, but real improvement has taken place since the early years of this experience at every age and among both males and females. The minor exceptions that are found in the table and the chart may be discounted as accidental or fortuitous. It is remarkable how drastically and consistently the death rates of diabetic patients have fallen. It will be noted that among children the death rate prior

to insulin occasionally exceeded 100% *per annum*. Actually, these extremely high rates represent a force of mortality rather than a true death rate, which cannot exceed unity. They indicate that the average duration of life among the children exposed in those age groups was less than a year after first observation. It is also clear that prior to 1914 the death rates among diabetics were highest at the very young ages. At that time the rates at every age up to 30 were much higher than those recorded between 70 and 80. Despite some improvement in the mortality of young diabetics in the Allen era, the death rates under 20 were generally higher than at all other ages, and between 20 and 30 were higher than between 30 and 70. With the introduction of insulin, however, there was a decided change for the better, and although very high rates still prevailed among the young diabetics, the rates were far lower than in the preceding eras. In the second part of the Banting era, the situation among young people improved still more, and for the first time the diabetic group yielded a mortality curve that was normal in respect to its shape, in that the lowest rates were recorded at younger ages and increased gradually through adult life.

The remarkable changes in the death rates among diabetics are shown in Table 2, which gives the percentage decline between successive periods and also between the first and last periods studied. The percentages at all ages combined were computed from death rates which were standardized on the basis of the total exposed to risk at each quinquennial age group from the beginning to the end of this experience. At all ages combined, the death rate in the second half of the Banting era was 74% less than in the Naunyn era. The death rate fell nearly one-third between the latter and the Allen era, but a much more rapid fall came as a result of the introduction of insulin, the death rate dropping 51% between the Allen and the first part of the Banting era, and 23% between the first and second parts of the latter era. These improvements apply to both males and females. The only notable difference is that the gains immediately following insulin were greater among females. Ultimately, however, the improvement as a result of the use of insulin has been about the same in both sexes.

Most impressive have been the declines among young diabetics. In the first two decades of life, the death rates in the second part of the Banting era were 98% below those in the Naunyn era. In other words, the rates in the later period were only about one-fiftieth of those prevailing prior to 1914. In the third decade, the drop was 95% and in the next two decades of life up to age 50 was over 80%. The smallest decline, 30%, was recorded in the eighth decade. In practically every instance, the rate of fall was greatest immediately after insulin was introduced. At ages under 30 the death rates in the early Banting era fell over 75%, that is, to levels less than one-fourth of those prevailing in the period immediately

preceding. Continued and marked improvement has taken place at all ages throughout the Banting era, but again these changes were most marked at the younger ages.

As the table shows, the rates of improvement by age have been about the same in each sex. The more rapid decline among females in the early Banting period was most distinct at ages under 40, but this was counterbalanced by the more rapid decline among males at these ages in the later Banting period.

TABLE 3.—EXPECTATION OF LIFE OF DIABETICS IN THE NAUNYN, ALLEN AND BANTING ERAS.* BY SEX. EXPERIENCE OF E. P. JOSLIN, 1897 TO 1929.

Age.	Expectation of life (years).							
	Males.				Females.			
	Naunyn.	Allen.	Banting.		Naunyn.	Allen.	Banting.	
			First part.	Second part.			First part.	Second part.
10 . .	1.1	2.8	10.8	33.2	1.5	2.4	17.8	30.2
15 . .	1.7	3.6	10.2	31.0	1.6	2.0	18.0	27.6
20 . .	2.4	4.6	11.0	28.2	1.3	1.8	18.8	24.7
25 . .	2.5	5.1	14.0	25.4	1.6	3.0	17.7	22.9
30 . .	4.5	6.5	16.3	23.1	3.7	6.0	17.4	22.4
35 . .	6.3	8.4	17.4	21.0	6.0	9.2	18.7	21.5
40 . .	6.7	9.7	16.3	18.5	8.6	10.4	18.1	19.3
45 . .	7.7	10.0	13.6	15.5	9.3	11.1	16.1	16.5
50 . .	8.0	8.6	11.2	12.9	8.0	10.5	13.4	13.6
55 . .	7.0	7.1	9.4	11.2	5.8	9.2	11.1	11.1
60 . .	5.1	6.0	7.7	9.4	4.2	7.2	9.4	9.1
65 . .	+	5.4	6.5	7.7	+	5.3	7.7	7.4
70 . .	+	5.1	5.6	6.0	+	3.4	5.4	5.8

* Naunyn, 1897–1913. Allen, 1914–August 6, 1922. Banting, first part, August 7, 1922–1925; second part, 1926–1928.

\+ Figures not reliable.

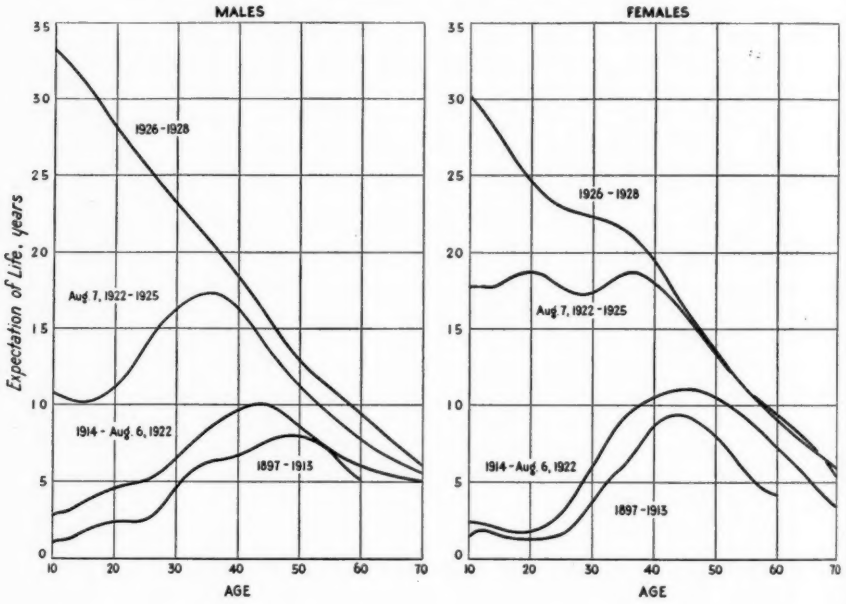
Comparative Mortality of Male and Female Patients. Male and female diabetics have approximately the same death rate. This is also brought out by Table 1. Prior to the discovery of insulin there was a moderate excess mortality among females, but with the discovery of insulin there was a sharp but temporary reversal in the relative mortality of the sexes. In the second part of the Banting era, however, the death rates at all ages combined were nearly identical.

There were, however, distinct variations by age. In all but one period the death rates of female patients under 40 have been generally higher than those for males. On the other hand, between 40 and 60 years of age, the death rates of male patients have been the higher. At ages over 60 the rates have been moderately close, except during the period immediately after insulin was introduced.

At that time the death rate of females at ages over 60 fell to a point 25% below that of males. It is notable that this is the only group in which the death rate in the second half of the Banting era showed no improvement over the earlier part.

The Expectation of Life of Diabetics. These striking reductions in the mortality of diabetic patients, of course, mean many added years of life. This is brought out clearly by Table 3 and Chart 2 which give the figures for their expectation of life, by age and sex, computed on the basis of the mortality rates shown in Table 1. These figures of expectation of life are presented as tentative and

CHART 2.—Expectation of life of diabetics in the Naunyn, Allen and Banting Eras. By sex and age. Experience of E. P. Joslin, 1897 to 1929.



approximate only. They apply, at any specific age, to the diabetic of average duration of the disease in the several epochs of this experience, and not to those with onset at the age. In constructing a life table, it is implicitly assumed that the persons at any specific age will, in the future, experience the death rates observed at the later ages. The situation among diabetics, particularly in the earlier periods of treatment and at the younger ages, does not strictly conform to this assumption. But as against this defect, it may be noted that at those ages where the death rates were extremely high (as, for example, the pre-insulin rates under age 30 in Table 1) the expectations of life were little affected by the death rates at

ages much removed. So far as duration of the disease exercises any effect on the death rates, we have found that, under recent conditions of treatment, this effect is relatively slight at the middle ages for durations up to 15 years. For longer durations there is as yet no adequate information. There are extremely few middle-aged diabetics whose disease began in childhood or early adult life. Practically all of them must be post-insulin cases because of the high death rate among young diabetics previously. Too short a time has elapsed since insulin came into use in 1922 for any large number of younger diabetics to attain middle life. By the very nature of the problem, it will take at least a decade to get a sizable experience on such cases.

TABLE 4.—RATIOS OF DEATH RATES AMONG DIABETICS TO THOSE AMONG PERSONS IN THE GENERAL POPULATION AT SPECIFIED PERIODS OF TIME.* SELECTED AGE GROUPS BY SEX. DIABETICS IN EXPERIENCE OF E. P. JOSLIN AND PERSONS IN THE ORIGINAL REGISTRATION STATES.

Sex; age.	Ratios (death rates of population = 1.)			
	Naunyn era.	Allen era.	Banting era.	
			First part.	Second part.
Males.				
5–14	260.9	129.9	18.7	1.8
15–24	92.0	56.0	36.8	5.0
25–34	40.8	35.7	19.9	5.5
45–54	7.1	6.3	4.1	3.4
65–74	4.2	3.0	2.3	1.8
Females.				
5–14	263.4	147.8	28.2	17.3
15–24	179.0	122.0	21.3	6.6
25–34	54.5	42.5	16.3	8.6
45–54	6.5	6.2	3.1	3.4
65–74	3.1	3.0	1.8	2.2

* Diabetics in Naunyn era *vs.* O. R. S., 1910; in Allen era *vs.* O. R. S., 1920; in Banting era *vs.* O. R. S., 1925.

Substantial gains in expectation of life have been made at every age, but most of all at the younger ages. Thus at age 10, the expectation of life of a diabetic boy in the Naunyn era was a little over a year. In the Allen era it jumped to nearly 3 years, increased sharply to nearly 11 years in the period immediately following the discovery of insulin, and increased extraordinarily again to 33 years after insulin had been in use 4 years or more. Altogether the gain in expectation of life for a diabetic boy of 10 was over 30 years. A slightly smaller gain was recorded for girls at this age. At age 20, the expectation of life of male diabetics has gone up from less than $2\frac{1}{2}$ years in the Naunyn era to over 28 years in the second part of the Banting era, an increase of nearly 26 years. The increase for

females was slightly less. At age 40, the expectation of life for both male and female diabetics has more than doubled between the two periods, with gains of over $11\frac{1}{2}$ and over $10\frac{1}{2}$ years for males and females respectively. Even at age 60, the expectation of life of males has increased $4\frac{1}{3}$ years, and that of females nearly 5 years.

Another interesting feature of the expectation of life figures is that prior to the discovery of insulin and even in the early years following that event, the age curve of expectation was grossly abnormal in shape. Normally, this curve is a steadily diminishing one, except during the first year or two of life when mortality rates are very high. In contrast, the earliest curves among diabetics show the highest expectation between 40 and 50 years of age. The two curves for males prior to insulin show increasing expectation from

TABLE 5.—COMPARISON OF EXPECTATION OF LIFE OF DIABETICS AND PERSONS IN THE GENERAL POPULATION AT SPECIFIED PERIODS OF TIME. SELECTED AGES BY SEX. DIABETICS IN EXPERIENCE OF E. P. JOSLIN AND PERSONS IN THE ORIGINAL REGISTRATION STATES.

Sex; age.	Expectation of life (years).							
	Diabetics, Naunyn era.	O. R. S., 1910.	Diabetics, Allen era.	O. R. S., 1919–1920.	Diabetics, Banting era, first part.	O. R. S., 1919–1920.	Diabetics, Banting era, second part.	O. R. S., 1929–1931.
Males.								
10	1.1	51.3	2.8	52.8	10.8	52.8	33.2	54.5
30	4.5	34.9	6.5	36.5	16.3	36.5	23.1	36.9
50	8.0	20.4	8.6	21.4	11.2	21.4	12.9	20.8
Females								
10	1.5	53.6	2.4	53.8	17.8	53.8	30.2	57.1
30	3.7	37.0	6.0	37.6	17.4	37.6	22.4	39.3
50	8.0	21.7	10.5	22.3	13.4	22.3	13.6	22.7

the youngest age in the table up to this maximum. The curves for females, after a slight initial decline also rise with age to a maximum in the 40's. In the first part of the Banting era, the male expectation of life increases up to age 35 before it begins declining, and the female curve fluctuates within a range of $1\frac{1}{2}$ years up to age 36, with maximum figures at ages 20 and 36, before it too declines in the normal manner. In the second part of the Banting era, the curve is entirely normal in shape, declining progressively from the youngest to the oldest ages.

Comparison With Population Tables. The great strides toward normality that the diabetics have made with respect to longevity are brought out by comparing the death rates and the figures for expectation of life of these patients with the data for the general population of the Original Registration States. The great majority of the patients in this experience were drawn from 8 of the 10 states,

which comprise this area, namely, the New England States, New York, and New Jersey. The comparison might also have been made with Massachusetts figures but the results would differ little. Population data for calendar years conveniently close to the several eras of treatment have been used.

Table 4 gives the ratios at selected ages of the death rates of these diabetic patients to the rates in the general population. This shows that in the Naunyn era, *i. e.*, prior to 1914, the death rates of diabetic patients between the ages of 5 and 14 were over 250 times the corresponding rates for the general population. Between ages 15 and 24, male diabetics had a death rate over 90 times that of the general population and female diabetics, nearly 180 times. The ratios decreased progressively with age so that at 65 to 74 they were only 4 times the general population rates for males and a little over 3 times for females. These ratios of the mortality of diabetics to that of the population have declined very drastically. With but unimportant exceptions each successive period of treatment showed lower ratios at every age. In the second part of the Banting period, the highest ratios recorded at the younger ages were under 6 in the case of males. They were generally higher in the case of females, notably between ages 5 and 14. At the older ages the death rates of diabetics in the Banting era were only about twice those in the general population..

Table 5, which gives the expectations of life at selected ages of diabetics and of persons in the Original Registration States, shows what large gains the decline in the preceding ratios mean when translated into expectations of life and, at the same time, how far the diabetic yet has to go to have a normal expectation for his age. For example, the diabetic boy of 10 of the Naunyn era had an expectation of life of scarcely one year, compared to an expectation of 51 years in the general population at that age. There was thus a loss of 50 years for the diabetic boy. Despite a sizable gain during the Allen era, there was just as great a gain in the population figure and consequently the deficiency remained at 50 years. With insulin, however, there was a marked increase in the expectation of life of the diabetic child and by the second part of the Banting period the expectation of life for a diabetic boy of 10 reached 33.2 years, as compared with 54.5 for males aged 10 in the Original Registration States during 1929 to 1931. Thus, the loss had been reduced to slightly over 20 years. At every age and both among males and females, the expectation of life of the diabetic patient has increased much faster since insulin than that of the general population and considerable progress has been made in reducing the deficiency in his expectation of life.

Summary. Life tables have been constructed for diabetic patients treated at the Baker Clinic during 1897 to 1928 and traced to 1929. These tabulations have been made in the same manner as survivorship experiences in insurance work. Only the period under observa-

tion was included, *i. e.*, from first consultation or hospital discharge. These tables give a definite measure of the improvement in the treatment of diabetes.

The outstanding facts are: 1. There has been a continuous decline in the death rate of diabetics.

2. The death rate at all ages in the latter part of the period surveyed, 1926 to 1929, was 75% below that of the first part, 1897 to 1913.

3. The gains have been greatest in young diabetics.

4. The decline in mortality was most rapid after insulin came into use.

5. Large increases in the expectation of life have occurred. At age 10, the increase between 1897 to 1913 and 1926 to 1929 is estimated at about 30 years. The increase is progressively less with advancing age.

6. The death rates of diabetics are still much in excess of those for the general population.

THE CREATINE TOLERANCE TEST IN THE DIFFERENTIAL DIAGNOSIS OF GRAVES' DISEASE AND ALLIED CONDITIONS.

By Arthur R. Sohval, M.D.,
clinical assistant physician, out-patient department,
Frederick H. King, M.D.,
adjunct physician,
and
Miriam Reiner, M.S.,
assistant chemist, the mount sinai hospital, new york city.

(From the Medical Service of Dr. George Baehr, and the Laboratories, The Mount Sinai Hospital.)

Ever since Shaffer[13] in 1908 reported significant creatinuria in patients with Graves' disease, occasional contributions to the study of creatine-creatinine metabolism in this disease have appeared. The more important of these include the observation of Palmer, Carson and Sloan[9] that creatinuria in Graves' disease disappears on the administration of iodine. More recently, Shorr[10,12] conceived the idea of putting a strain on the mechanism controlling creatine metabolism by causing the patient to ingest a known quantity of creatine. In this manner, the degree of excretion could be determined and a creatine tolerance test was devised.

Before describing the test and the clinical material forming the basis of this report, a short discussion of creatine-creatinine metabolism is presented.

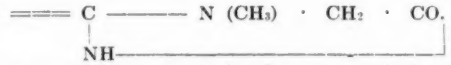
Creatine. Creatine is methylguanidine acetic acid, whose chemical formula is

$$HN = C(NH_2) - N(CH_3) \cdot CH_2 \cdot COOH$$

About 98% of the total amount in the body occurs in muscle, particularly striated, and most of the remainder in the brain. It is presumably derived from protein. Fiske and Subbarow[2] have shown that a large part of creatine in muscle is present in combination with phosphoric acid as phosphocreatine.

Creatine is present in the blood in very low concentration. It is claimed to be normally absent in the urine of human adults except during menstruation, gestation, and lactation; it may also be present during starvation and as a result of the ingestion of a high-animal protein or low-carbohydrate[7] diet. Creatinuria likewise is present in febrile and acidotic conditions, in hyperthyroidism, creatinism, infantilism, diabetes, achondroplasia, poliomyelitis, myositis, and other muscle diseases such as atrophy and dystrophy.[1]

Creatinine. Creatinine is the internal anhydride of creatine with the formula



Creatine can be converted to creatinine by removal of one molecule of water through treatment with hot acid solutions. The amount of creatinine in the 24-hour urine of normal adults ranges from .500 to 2.000 gm. Except for diet and exercise, it is a constant characteristic of a given normal individual,[3a] being determined by size and muscular development. For this reason, the total creatinine excretion is frequently employed as a means of checking the accuracy of 24-hour urine collections. Thus creatinine is apparently an end-product of creatine metabolism and merely represents a waste product. Ingestion of the substance results in almost quantitative excretion in the urine. This is in contrast to creatine, ingestion of which by normal adults results in about 70% retention.

Creatinine is increased in the urine in fevers and decreased in hyperthyroidism, diabetes and conditions of profound muscular weakness. It appears to be compensatorily lowered in the presence of spontaneous creatinuria.

Creatine Tolerance Test. The creatine tolerance test[10,12] was devised to determine the ability of persons on a creatine-free diet to retain ingested creatine. According to Shorr, evidence of a defect in the metabolism of this substance is indicated by: 1, spontaneous creatinuria above 50 to 60 mg. per 24 hours; 2, retention of less than 70% of the ingested creatine; 3, low output of creatinine per kilo of body weight.

Technique. The patient is placed on a creatine-free diet* for 4 days. During the third day he collects the entire urinary output for 24 hours under thymol. He then takes 1.32 gm. of creatine hydrate (equivalent to 1 gm. of creatine in the urine expressed as creatinine) dissolved in 180 cc. of water and the urine is again collected for 24 hours under thymol. The

* No fowl, fish in any form, meat or meat products such as soups, cocoa or chocolate.

entire urinary output for the control-day and the creatine-day is then analyzed for creatine and creatinine.

Method for Determination of Creatine and Creatinine. The method for the determination of creatine and creatinine was a slight modification of Folin's[3b]

Measure the volume of urine and pipette 2 cc. of the specimen (the amount required varies according to the creatinine in the specimen; it may be necessary to repeat with 1 to 5 cc.) in 100 cc. volumetric flask for preformed creatinine, and 2 cc. in 250 cc. Erlenmeyer for the "total creatinine."

To the Erlenmeyer flask add 20 cc. of saturated solution of very pure picric acid, an antibump tube, and record the weight of the flask and contents. Add about 150 cc. of distilled water and boil on an electric hot-plate until the flask and contents weigh about the original amount.

Compare both the "total creatinine" and preformed creatinine with standards containing 1 and 2 cc. of standard creatinine solution (containing 1 mg. of creatinine per cc.) in 100 cc. flasks. To standards and urine for creatinine add 20 cc. saturated picric acid. To all flasks add 1.5 cc. of 10% sodium hydroxide solution, and after 10 minutes transfer the hydrolyzed specimens from the Erlenmeyer flask to 100 cc. flask. Make up to mark with water and read immediately in colorimeter with the appropriate standard set at 10 mm.

The hydrolyzed specimen contains "total creatinine"—preformed and hydrolyzed creatine. The unhydrolyzed specimen contains preformed creatinine. So-called creatine is the difference between the total and unhydrolyzed specimens.

The creatine excreted on the second or creatine-day minus that excreted on the first or control day gives the amount of extra creatine excreted. This divided by the total amount of creatine which might have been excreted (1 gm.) gives the percentage excretion from which the retention is easily calculated. Normal adults are said to retain 70% or more.

Clinical Data. In order to determine the usefulness of the creatine tolerance test, it was performed in 75 patients with one or more of the following conditions: Graves' disease, autonomic imbalance, menopause, hypertension, non-toxic goiter and psychoneurosis. The patients were studied chiefly in the Out-Patient Department and were subjected to 102 tests. The individuals were classified in the following groups:

	No. of patients.	No. of tests.
Graves' disease	15	27
Autonomic imbalance	42	57
Menopause with autonomic imbalance and hypertension	7	7
Essential hypertension	6	6
Non-toxic goiter	5*	5*
Psychoneurosis	1	1
	75	102

* One is included in the hypertension group.

At times the clinical diagnosis was not readily apparent and the patients required variable periods of observation. This was particularly true in the differentiation of Graves' disease from autonomic imbalance where it was sometimes necessary to hospitalize the patient for this purpose. The attending physician in charge of the service corroborated the final diagnosis in all such patients.

Many precautions were taken to insure accuracy on the part of the patient in performing the test. The creatine-free diet and the manner of collection of the urine specimens were explained to each patient in great detail. The patients were greatly impressed with the amount of attention they received and were uniformly coöperative and conscientious in the execution of the

tests. In addition, they received printed instructions on the reverse side of which they were requested to keep a diary of the food eaten daily. When the patient brought the urine specimens back to the hospital, his accuracy

TABLE 1.—GRAVES' DISEASE.

Case No.	Sex.	Age.	Basal metabolic rate.				Creatine tolerance test.				
							Creatine in grams per 24 hours.		Creatinine in grams per 24 hours.		Retention, %.
							Control day.	Creatine day.	Control day.	Creatine day.	
57	M	35	+59	+41	+52	+6*	0	0.050	0.640	0.950	95
58	M	52	+37	+31	*+20*	*+10*	.185	.210	.880	.750	98
			+28	*+13*	−8	+31	.075	.365	.800	.390	71
			+31	+41	+50	*+29*					
			+31	+9†							
59	F	58		+48	*+17*		.145	.775	.670	.615	37
60	F	45	+66	+52	+48	*+42*	0	.210	.570	1.170	79
			+25	+43	+24		0	.190	.740	.945	81
							.455	*.905*	*.365*	*.795*	*55*
							0	.305	.805	.800	69
62	F	21	+35	+49	*+37*	*+21*	*.440*	*.705*	*.530*	*.445*	*74*
			+8	+50	0†	+25	.100	.400	.710	.850	70
63	F	19	+15	+54	*+62*	*+64*	.050	.400	.435	.670	65
			+38	*+13*†	*+9**		.180	.695	.815	.695	48
							.095	.115	.755	.785	98
64	F	56	+36	+29	+20		.045	.560	.450	.560	49
65	M	42	+60	+16	+51	*+60*	.175	1.190	1.150	.970	−1
			+45†	*+15*†	+4*	+9*	.025†	.645	...	...	38
							0*	.125	.840	.900	87
66	F	69	+51	+29	+43	*+34*	.390	1.885	.755	.765	−60
			+24	*+29*	*+22*	*+13*†	*.320*	*.390*	*.700*	*.665*	*93*
			+22	*+20*	+7	+47	*.305*†	*.340*	*.765*	*.790*	*97*
			−4	+23			.096†	.380	.720	.710	72
67	F	30	+62	+48	*+11*	*+28*	.260	.395	1.060	1.045	86
			+43	+48	+19†						
			INACTIVE GRAVES' DISEASE. *Asymptomatic.*								
68	F	31		−13			.130	.420	.790	.830	71
69	F	38	+66	+37	+43	+31	0*	.175	.920	.975	82
			+45	+54	+27	+25*					
			INACTIVE GRAVES' DISEASE. *Symptomatic.*								
70	F	27		+9	−4		.055	.210	.775	.675	85
71	F	39			+14		.050	.815	.975	.895	23
73	F	48	+48	+47	−10	+6	0	.055	.900	.850	94
			−10	−6							

Figures in italics indicate determinations made during a hospital stay as an in-patient.

* Postoperative. † After lugolization.

was checked by a complete recital of the manner in which the voidings were collected. Tests were discarded in the event of error. While we occasionally noted the presence of significant variations in the output of creatinine in the 2 test days, we were prompted to include these tests for two reasons; first, because of our conviction regarding the reliability of the urine collections and second, because of the possibility that such variations may be inherent in the diseases investigated. Whenever possible attempts were made to repeat positive tests. Care was taken to exclude patients with acetonuria or with those physiologic and pathologic states known to induce creatinuria.

Shortly after this work was started, and in accordance with the experience of our Department of Chemistry, spontaneous creatinuria was not held to be abnormal nor was it so designated unless the creatinine exceeded 100 mg. in 24 hours. Tolerance to the ingested creatine was regarded as decreased when the retention was less than 70%. The finding of spontaneous creatinuria *or* decreased tolerance is referred to as a *partially* positive test while the presence of both indicates a *completely* positive test.

Graves' Disease. There were 15 patients in this group (Table 1), 10 active and 5 inactive as a result of operation or roentgentherapy. Of the 5 inactive cases, 3 were still symptomatic in that they still complained of nervousness, emotional and vasomotor instability and weakness, although the basal metabolic rates were normal and they had gained weight. The remaining 2 inactive cases were completely asymptomatic.

Of 10 patients with active Graves' disease, subjected to 22 tests, 8 had spontaneous creatinuria (Table 2). In 2 of these 8, it was

TABLE 2.—RESULTS OF CREATINE TOLERANCE TEST.

	Graves' disease.		Autonomic imbalance (49 cases).	Hypertension *or* goiter *or* psychoneurosis (11 cases).
	Active (10 cases).	Inactive (5 cases).		
Spontaneous creatinuria	8	1	16	2
Confirmed by 2d test	2		4	0
Unconfirmed by 2d test	3		6	2
Decreased tolerance	6	1	18	1
Confirmed by 2d test	2		2	0
Unconfirmed by 2d test	3		6	1
Spontaneous creatinuria *or* decreased tolerance	9	2	27	2
Spontaneous creatinuria *and* decreased tolerance	5	0	5	0
Confirmed by 2d test	..		1	
Unconfirmed by 2d test	3		3	

present and in 3 others of these 8 it was absent on a second determination without the use of iodine. Six patients showed a decreased creatine tolerance. In 2 of these 6 it was present and in 3 it was absent on a second determination without the use of iodine. Spontaneous creatinuria *or* decreased tolerance was demonstrated in 9 patients, whereas *both* spontaneous creatinuria and decreased tolerance were found in 5. In 3 of these 5 patients, however, another test was entirely normal.

Of 3 patients with inactive, but symptomatic, Graves' disease, none showed spontaneous creatinuria while one revealed decreased

TABLE 3.—AUTONOMIC IMBALANCE.

Case No.	Sex.	Age.	Basal metabolic rate.	Creatine tolerance test.				
				Creatine in grams per 24 hours.		Creatinine in grams per 24 hours.		Retention, %.
				Control day.	Creatine day.	Control day.	Creatine day.	
2	F	39	+37 +65 −15	0.135	0.415	0.670	0.605	72
3	F	35	...*	.055	.635	.970	.720	42
4	F	30	+4	0	.090	.900	.960	91
5	F	26	−10	0	.330	.640	.385	67
				.030	.135	.365	.240	89
6	F	46	+38 +15	.160	.730	.800	.970	43
				.230	.330	.860	.900	90
7	F	31	+33†	.265	.330	1.150	.850	94
8	F	36	+11 +43	.105	.780	.535	.580	33
9	F	29	+42 +13	0	.630	1.270	.930	37
10	M	30	+3	.095	.190	1.845	1.160	91
11	F	45	+3	0	.360	.500	.530	64
12	F	59	+45 *−2*	0	.165	.750	.505	83
13	M	36	−3	0	0	1.040	1.280	100
14	F	37	+24 +23 +36 +15	.055	.700	1.275	1.240	36
15	F	40	+9	0	.125	.955	1.290	87
				.695	1.000	1.270	1.240	70
16	M	35	+22 +42 +23 *+17*	*.070*	*.655*	*.910*	*.990*	*41*
			+10 +5 +4 *+2*	*0*	*.180*	*1.310*	*1.950*	*82*
			+31 +25 +14	0	.335	1.590	1.850	66
17	F	45	+36 +49 *−20* *+5*	0	.245	1.220	1.165	75
			+31 +11					
18	M	44	+17 +1	.285	.340	.940	.785	95
				.180	.190	.835	1.690	99
19	F	44	0	.090	.380	.800	.710	71
21	F	26	+114† +31 +40 +17	0	.135	.560	.830	86
			+47 +3 +5					
22	F	29	+64 *+37* *+30* *+19*	*.170*	*.220*	*.440*	*.245*	*95*
			+25 *+20* +5	*.155*	*.605*	*.580*	*.660*	*55*
				0	.170	.880	.680	83
23	F	59	+33 +2 −6 +1	.595	.935	.895	.945	66
				.210	.875	.855	.875	33
24	F	30	+11 −11	0	.150	.790	.620	85
25	F	19	−3	0	.120	.740	.690	88
26	F	31	+46 +30 +35 +21	.200	.370	1.470	1.120	83
			+54 +23 *+9*	0	.170	1.130	1.090	83
27	F	33	+22 +38 +15	.145	.445	.835	.810	70
				0	.280	.870	1.050	72
29	F	25	+28 +14	0	.120	.850	1.060	88
32	F	29	+71 +37 +29 *+9*	.060	.495	.750	.825	56
33	F	38	+12	.055	.120	1.110	.795	94
34	F	29	+16 +43 +2	.040	.080	.740	.980	96
35	F	40	+2	.070	.420	.620	1.400	65
36	F	74	+41 +30 +16	.120	.100	.470	.660	102
				0	.450	1.200	1.200	55
38	F	28	−5 +19	.055	.090	.730	.660	97
39	M	40	+42 +4	.135	.320	1.025	1.470	82
				0	0	1.450	1.640	100
40	F	37	+23 0	.165	.520	.985	.860	65
				0	.295	.960	.835	70
41	M	43	+21 −16	.355	.490	1.415	.730	87
42	F	33	+30 +18 0	0	.180	.730	.650	82
43	F	40	+10	.295	.535	.875	.805	76
				.080	.340	.500	.430	74
44	F	64	+20 +23 +20 +10	.065	.195	.745	.885	87
45	F	33	+30 +45 +2	.130	.400	.830	.600	73
47	F	38	+28 +12 +43 +26	.060	.180	.770	1.090	88
48	F	55	+20 +20 0	0	0	.850	1.330	100
49	F	42	*+21* *+16* −8 +31	0	.365	.625	.475	63
			+18 +56 −2					

Figures in italics indicate determinations made during a hospital stay as an in-patient.
* Patient was too nervous to complete the test. Obviously not a case of Graves' disease. † Obviously a false reading. Clearly not Graves' disease.

tolerance. Of the 2 inactive, asymptomatic cases, 1 disclosed spontaneous creatinuria while neither had a decreased tolerance.

Autonomic Imbalance. The patients in this group form a clinical entity which has been variously designated in the literature as "forme fruste" of hyperthyroidism, larval hyperthyroidism, Basedowoid, neurocirculatory asthenia, and Graves' constitution.[8] Kessel and Hyman[6] applied the term "autonomic imbalance" to this group of patients "whose symptoms can be ascribed to a disturbance in the realm of the involuntary nervous system. . . . Manifestations of the disturbance have been present in most of these patients as far back as they can remember."

The symptomatology is referable to that organ system whose involuntary innervation is disturbed. The dominant manifestations may thus be neuropsychiatric, circulatory, cardiac, gastro-intestinal or any combination of these. The commoner features of this syndrome consist of palpitations, dyspnea, tachycardia, labile pulse rate, tremor, sweating, vasomotor and emotional disturbances, nervousness, asthenia, anxiety states, diarrhea, "indigestion," menstrual disturbances, headache and insomnia. Non-toxic goiter is not infrequently present with such profound vasomotor disturbances as to simulate Graves' disease very closely. Even in the absence of goiter, differentiation from Graves' disease often requires prolonged observation. At times, hospitalization and patient effort to secure the subject's confidence is necessary in order to obtain accurate basal metabolic and pulse rates. Failing this, a therapeutic test with iodides usually aids in differentiation.

This group numbered 42 patients who were subjected to 57 tests (Table 3). Spontaneous creatinuria (the highest was 695 mg.) was found in 16 patients. In 4 of these, this was confirmed by a second test, while in 8, confirmatory results could not be obtained. Decreased tolerance was revealed in 15 patients. It was present in 2 and absent in 6 on a second determination. Either spontaneous creatinuria *or* decreased tolerance was disclosed in 24 patients. Spontaneous creatinuria *and* decreased tolerance were noted in 5 patients. The test was repeated in 4 of these and provided confirmation in but 1. A completely normal result was obtained in another. In 2 others, spontaneous creatinuria was again demonstrated but this time with normal tolerance. Three tests performed in 1 patient (Case 22) gave widely different results, ranging from completely normal to completely abnormal.

Menopause with Autonomic Imbalance and Hypertension. Autonomic imbalance is frequently observed in association with menopausal symptoms and hypertension, the latter usually of recent origin. In addition to menopausal vasomotor disturbances such as hot flashes, sweats and dizziness, this group of patients presents manifestations of dysfunction in the autonomic nervous system as outlined above. Here again differentiation from Graves' disease is occasionally difficult.

TABLE 4.—MENOPAUSE WITH AUTONOMIC IMBALANCE AND HYPERTENSION.

Case No.	Basal metabolic rate.	Creatine tolerance test.				
		Creatine in grams per 24 hours.		Creatinine in grams per 24 hours.		Retention, %.
		Control day.	Creatine day.	Control day.	Creatine day.	
50	+21 +18 +5	0	0.365	1.065	1.100	63
51	+9 +5	.055	.410	1.275	1.090	64
52	+15 +35 +61 +12	.080	.200	.530	.695	88
53	+16 +41 +13 +48 +15 +32 +31 +38 +33	.045	.130	.880	.725	92
54	+9	.070	.100	.790	.905	97
55	+35 +26	0	.020	1.050	.720	98
56	+36 +25 −3 −5	.070	.390	1.250	1.060	68

There were 7 cases in this group (Table 4). By the creatine tolerance test, spontaneous creatinuria was absent in all, while decreased tolerance was found in 3.

TABLE 5.

Case No.	Sex.	Age.	Basal metabolic rate.	Creatine tolerance test.				
				Creatine in grams per 24 hours.		Creatinine in grams per 24 hours.		Retention, %.
				Control day.	Creatine day.	Control day.	Creatine day.	
			Essential Hypertension.					
75	M	15	−28 −3	0	0.165	0.920	1.025	83
76	M	55	+25 +10 +19	0	.280	1.350	1.210	72
77	F	60	+27 +25 +20 +24 +12	0	.205	.925	.990	79
79	F	48	+31 +14	.015	.020	.365	.415	100
80	F	42	+26 +10	0	.190	1.055	1.090	81
83	F	44	0	.050	.100	.920	.535	95
			Non-toxic Goiter.					
77	F	60	+27 +25 +20 +24 +12	0	.205	.925	.990	79
84	F	15	+27 +6	0	.275	.890	.665	72
85	F	48	+18	.255	.380	1.670	1.220	87
				.070	.335	1.235	1.000	73
86	F	26	+13 +18	.330	.350	.650	.960	98
				.090	.530	.670	.625	56
87	M	18	−1	.070	0	1.360	1.775	107
			Psychoneurosis.					
91	F	32	−24	.060	.265	.305	.370	79

The results of the creatine tolerance test in this and the preceding group of cases of autonomic imbalance were combined (Table 2). Of the total number of 49 cases, spontaneous creatinuria occurred in 16 patients, decreased tolerance in 18, spontaneous creatinuria *or* decreased tolerance in 27 and spontaneous creatinuria *and* decreased tolerance in 5.

Hypertension or Non-toxic Goiter or Psychoneurosis. A group of 11 "non-nervous" patients was likewise subjected to the creatine tolerance test. These groups were selected because they are allied to the previous groups and yet may serve as controls.

The test was completely normal in 6 cases of hypertension (Table 5). Of 5 patients with non-toxic goiter (one was included in the hypertension group), spontaneous creatinuria was found in 2, but could not be confirmed by a second determination. One patient showed decreased tolerance which also could not be confirmed. Spontaneous creatinuria *or* decreased tolerance was present in 2 patients. The test in 1 patient with psychoneurosis was normal. Thus, of 11 patients, unconfirmed spontaneous creatinuria was found in 2, unconfirmed decreased tolerance in 1 and spontaneous creatinuria *or* decreased tolerance in 2. In no case were both spontaneous creatinuria *and* decreased tolerance present (Table 2).

Discussion. Our experiences with the creatine tolerance test are at variance with those recorded by Shorr and Thorn.[15] In the first place, only one-half of our active cases of Graves' disease gave a *completely* positive test. Attempts at confirmation of the positive test failed in each of 3 patients. On the other hand, a partially positive test (spontaneous creatinuria *or* decreased tolerance) occurred in 90% of these patients. Here again, however, when the test was repeated, confirmation was usually not obtained.

Shorr,[11] in reviewing our protocols, drew attention to the possibility of an unsuspected source of iodine, such as iodized salt, as an explanation for the absence of spontaneous creatinuria in some cases of Graves' disease. This cannot be denied but we feel that it is not of very great moment, inasmuch as Kepler and Boothby[5] found creatinuria in only 84% of 25 patients with Graves' disease who had not received iodine and in 60% of 115 similar patients of whom nearly two-thirds had received iodine. The former finding corresponds to our finding of 80% incidence of creatinuria in non-iodized Graves' disease.

The group of non-nervous patients comprising hypertension, non-toxic goiter or psychoneurosis, although small, may serve as a control series. Kepler and Boothby[5] have previously reported creatinuria in 11% of their cases of benign adenoma and in 14% of control cases. Tolerance tests were not performed by these workers.

In our series a *completely* positive test was not encountered in any case. A definite percentage, however, showed a *partially* positive test. Again, this was more often unconfirmed than confirmed.

Doubt is thus seriously cast upon the significance of partially positive results. In this connection, the work of Taylor and Chew[14] suggests that the occasional finding of spontaneous creatinuria in normal persons may be due to sudden, but not necessarily extreme, change in muscular activity.

The outcome of the test was most interesting in the group of patients with autonomic imbalance. More than one-half showed a *partially* positive test while in 10% a *completely* positive test was obtained. Thus, with respect to defects in creatine metabolism, this group occupies a position which is roughly midway between Graves' disease on the one hand and normal persons on the other (Table 2).

From our results it is apparent that this test is not constantly positive or pathognomonic in patients with Graves' disease. Furthermore, the occurrence of *partially* positive tests in a control series and *completely* positive tests in autonomic imbalance detracts from the usefulness of the test in differentiating borderline cases. Shorr contends that the specificity of the test in Graves' disease dwells in the disappearance of the positive test under iodinization. While we do not deny the fact that iodinization diminishes creatinuria in Graves' disease, our protocols indicate that a positive test, regardless of the disease, usually disappears spontaneously. On the other hand, our studies indicate a relationship between autonomic imbalance and Graves' disease which was postulated by Hyman and Kessel[4] but heretofore factually unconfirmed. It is their contention that Graves' syndrome represents a superimposition of hyperthyroidism on a fundamental imbalance of the autonomic nervous system. This is in keeping with the almost universally elicited detail in the history of patients with Graves' disease to the effect that the individual was "always nervous," "highstrung," "unstable," or neurotic. Of the 86 cases of autonomic imbalance studied by them, 1 patient was observed to pass into Graves' disease. Our own series is too small and the period of observation too short to permit comment on the incidence of this transition. However, the occurrence of the same metabolic defect (completely positive creatine tolerance test) in autonomic imbalance as in Graves' disease points to a fundamental relationship between the two. The fact that the defect occurs more often in the latter is due to the added thyroid disturbance.

Summary and Conclusions. 1. The creatine tolerance test as devised by Shorr was performed in a group of patients with one or more of the following conditions: Graves' disease, autonomic imbalance, menopause, hypertension, non-toxic goiter and psychoneurosis.

2. A small percentage of partially positive tests (18%) was encountered in the "non-nervous" control series composed of hypertension, non-toxic goiter and psychoneurosis.

3. A greater incidence of partially positive tests (37%) and a 10% occurrence of completely positive tests was encountered in the group of patients with autonomic imbalance.

4. The greatest frequency of positive tests (90%) was observed in the group with active Graves' disease.

5. Whereas a completely positive tolerance test may be useful in differentiating Graves' disease from a condition which does not at all simulate it, the efficacy of the test in the differential diagnosis of borderline cases, *i. e.*, autonomic imbalance, is sharply curtailed by the following observations; the occurrence of partially positive tests in control series and of completely positive tests in patients with autonomic imbalance; the occurrence of completely positive tests in *only* one-half of our patients with active Graves' disease.

6. The occurrence of completely positive creatine tolerance tests, indicative of a defect in creatine metabolism, in autonomic imbalance and Graves' disease suggests a fundamental relationship between the two.

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THE COEXISTENCE OF MYXEDEMA AND PELLAGRA IN THE SAME PATIENT.

With Report of Two Cases.

By James A. Greene, M.D.,

Assistant Professor, Department of Theory and Practice, University of Iowa Medical School, Iowa City, Iowa.

(From the State University of Iowa Medical School.)

The coexistence of pellagra and myxedema has not been reported as such in the literature. Either disease may be overlooked if the two coexist because of the similarity of the gastro-enteric, psychic, neurologic, and to a less degree, the dermatologic manifestations of the two maladies. Such an oversight may lead to a fatality, whereas otherwise recovery might be expected. It is for this reason that the following 2 cases are reported.

Case Reports. Case 1. A white married female, aged 53, entered the University Hospitals complaining of soreness of mouth, diarrhea, dryness of skin and hair, loss of the use of her legs, and mental changes. The history was questionable because of psychosis, but the general facts were confirmed by the family. She had always enjoyed good health and had reared 5 children. The present illness began 11 years before admission. The initial subjective manifestations consisted of increasing obstipation, weakness, drowsiness, intolerance to cold, absence of sweating, dryness of skin and hair, with loss of the latter from the axillæ, being suspicious of others, slowness of speech, and huskiness of voice. During the past 6 months soreness of mouth, diarrhea with 6 to 7 watery stools daily, dermatitis confined to the exposed areas, slight bilateral deafness, a vague paresthesia which progressed to abasia, and hallucinations appeared. The dietary history was of no value.

She was a well developed and nourished woman of about the stated age, who coöperated well and answered questions freely. The significant objective manifestations were slowness of speech, huskiness of voice, dryness and coarseness of hair which was absent from the axillæ, dryness of skin, brownish dermatitis over anterior legs and over dorsum of hands and forearms, slight bilateral deafness, marked stomatitis, enlargement of tongue with atrophied papillæ, cardiac rate of 70 beats per minute, arterial pressure 100/70, moderately distended abdomen, hemoglobin of 65%, erythrocytes 2.5 million, leukocytes 5200, achlorhydria, and a basal oxygen consumption of 45% below normal. Sluggish reflexes were the only neurologic finding in spite of the abasia. Blood agglutination reactions were negative for typhoid, paratyphoid, melitensis, and dysentery bacilli. There was no gross or occult blood in the stools and direct and cultural examinations revealed no pathogenic organisms. Roentgen-ray examination of the colon by barium enema showed a large atonic bowel.

Course. In order to ascertain which of the manifestations could be attributed to myxedema and which to pellagra, the hypothyroidism was controlled by the administration of desiccated thyroid gland and the pellagra permitted to continue by feeding a diet low in vitamins. The basal oxygen consumption increased to 2% above normal at the end of 3 weeks, and the weakness, drowsiness, and intolerance to cold subsided. Sweating appeared and the speech improved. The psychosis improved remarkably, but the diarrhea, stomatitis, and dermatitis persisted.

A high-caloric, high-vitamin diet with added vitamin B, and a maintenance dose of desiccated thyroid gland were then prescribed. She ate fairly well and during the next 5 weeks the dermatitis and stomatitis disappeared, the mental condition continued to improve, but the diarrhea persisted. During the next 12 weeks, in spite of large amounts of liver extract parenterally and yeast and liver extract orally, the psychosis returned, delusions and hallucinations appeared, and all attempts to maintain an adequate food intake failed. She lost body weight and the mental condition necessitated that she be transferred to the Psychopathic Hospital. The appetite immediately improved and during her stay of 3 weeks she gained strength and body weight, and the diarrhea subsided. The psychosis, however, continued and she was transferred to the State Hospital for the Insane. The psychosis gradually subsided and after 3½ months she was permitted to return home. A report by letter after 4 months at home stated that she felt well and was doing her own housework.

Case 2. A white married female, aged 38, entered the University Hospitals complaining of weakness. She was emotionally unstable and suspicious. The history, therefore, was not as accurate as desired. She had always considered herself well until the present illness which began 6 years before admission to the hospital. The subjective manifestations

noted during the first 4 years of her illness were weakness, being suspicious of others, and intolerance to cold. These symptoms became more pronounced during the last 2 years and were accompanied by amenorrhea, shortness of breath upon exertion, thickness and soreness of tongue, anorexia alternating constipation and diarrhea which changed to continuous diarrhea for the last 2 months, loss of body weight, clumsiness, ataxia, paresthesia of the feet and fingers, increase of mental symptoms, dryness of skin, and a brownish dermatitis over dorsum of hands and feet which appeared upon exposure to sunlight. She had received some "liver capsules" and intramuscular injections of liver extract without improvement. The dietary history was unreliable.

She was a well developed and emaciated white woman of about the stated age who coöperated poorly and answered questions reluctantly. The significant objective manifestations were slowness of speech, huskiness of voice, puffiness of face, broadening of nose, thickness of lips, dryness and coarseness of hair which was sparse over the trunk and extremities, dryness and coarseness of skin, brownish dermatitis over dorsum of hands and forearms and over dorsum of feet except for areas across the feet covered by the straps of her shoes, moderately severe stomatitis, enlarged and inflamed tongue, cardiac rate of 70, arterial pressure of 105/75, hemoglobin 72%, erythrocytes 3.0 million, leukocytes 4600, achlorhydria, occult blood in 7 of 9 stool examinations, and a basal oxygen consumption of 32% below normal. Stool examinations both direct and cultural revealed no pathogenic organisms. Blood agglutination reactions were negative for typhoid, paratyphoid, melitensis, and dysentery bacilli.

Course. In this patient the order of the specific therapy was the reverse of that of the previous case, and was concerned with the control of the pellagra through the administration of a high-caloric and high-vitamin diet with added vitamin B. The stomatitis, dermatitis, and diarrhea subsided. The appetite, strength, and body weight increased during the 3 weeks of this régime, but the psychosis was unchanged. The myxedema was then controlled by the addition of desiccated thyroid gland. The basal oxygen consumption increased to 5% above normal after 3 weeks. Sweating returned, intolerance to cold disappeared, and the speech and strength improved remarkably, but she continued to be somewhat suspicious of others and emotionally unstable.

Comment. The myxedema preceded the pellagra by several years in both cases. Certain manifestations of the former disease may have facilitated the production of the latter. The psychic and gastro-enteric disturbances resulting from the myxedema undoubtedly were factors in the prevention of an adequate food intake in the 2 cases. Gastric dysfunction has been considered as an etiologic factor in pellagra.[3] The frequent occurrence of achlorhydria and the small amount of gastric secretion obtained in some cases are evidence for gastric dysfunction in myxedema. Furthermore, the absence of the intrinsic factor of Castle[1] in 1 of 2 cases of myxedema previously reported[2] shows that gastric dysfunction may occur.

The psychic, neurologic, gastro-enteric, and to a less extent, the dermatologic disturbances which may be present in a case of coexisting myxedema and pellagra may be attributed to either disease. The 2 cases here presented did not have any demonstrable neurologic lesions. The psychic disturbances in both cases antedated the other

symptoms of pellagra by several years and were due to myxedema until the onset of pellagra when the psychosis became increased. Both diseases were apparently contributing factors in the mental condition of both patients at the time of admission to the hospital. It is impossible, however, from the data available to state which of the two diseases played the dominating rôle. The presence of psychosis does not appear to alter the prognosis in myxedema, whereas it does in pellagra. The response to therapy by the 2 patients indicate that the presence of mental changes produced by the coexistence of the two diseases does not necessarily signify a grave prognosis.

Diarrhea is common in both diseases, but in myxedema it usually alternates with constipation. The continuation of diarrhea in Case 1 after the thyroid deficiency had been controlled and its termination in Case 2 before the administration of desiccated thyroid gland signifies that pellagra was the etiologic factor in both instances.

Dermatitis may develop in myxedema and in both instances this possibility was considered. The skin lesions in 2 previous cases in which dermatitis was thought to be due to myxedema were generalized and were not aggravated by exposure to sunlight. The typical character, distribution, and response to therapy of the dermatitis present in the 2 cases of this report indicate that pellagra and not myxedema was the etiologic factor.

Stomatitis and glossitis are common in pellagra, whereas they do not occur in myxedema without a vitamin deficiency. The glossitis observed in 3 cases of myxedema previously reported[2] was attributed to a vitamin B deficiency and suggested that deficiency diseases may develop in myxedema.

The relation of thyroid therapy and of antipellagra treatment to the disappearance of manifestations of the two diseases in both cases are shown in Table 1.

TABLE 1.—SYMPTOMS BEFORE AND AFTER TREATMENT.

	Case 1.			Case 2.		
	Before Rx.	After thyroid.	After antipellagra Rx.	Before Rx.	After antipellagra Rx.	After thyroid.
Intolerance to cold	+	0	0	+	+	0
Absence of sweating	+	0	0	+	+	0
Dryness of skin	+	0	0	+	+	0
Loss of hair	+	+	+	+	+	+
Slowness of speech	+	0	0	+	+	0
Huskiness of voice	+	0	0	+	+	0
Stomatitis	+	+	0	+	0	0
Dermatitis	+	+	0	+	0	0
Diarrhea	+	+	0	+	0	0
Paresthesia	+	0	0	+	+	0
Psychosis	+	+	0	+	+	±
Anemia	+	+	..	+	+	
Achlorhydria	+	..	..	+		
BMR	−45	+1	−5	−32	−32	−3

The development of pellagra in cases of myxedema emphasizes that deficiency diseases are likely to develop in any chronic malady, particularly if there are long standing gastro-enteric or psychic derangements.

Summary. The coexistence of pellagra and myxedema have not been described previously. Two such cases are reported. A fatal termination is almost certain if both diseases are not recognized. The manifestations of the myxedema which may facilitate the production of pellagra are discussed. An attempt was made in the 2 cases to ascertain which disease was responsible for production of manifestations which may be common to both maladies.

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THE SPECTROGRAPHIC DETERMINATION OF LEAD IN BLOOD FROM NORMAL HUMAN SUBJECTS.*

By Gordon H. Scott,

and

J. Howard McMillen,

St. Louis, Mo.

(From the Department of Anatomy, Washington University School of Medicine.)

It is of some general interest to know the distribution of a toxic substance such as lead in a population relatively unexposed to the metal as an industrial hazard.

Clear-cut data regarding the normal distribution of lead in the blood are exceedingly hard to secure. Most cases in which such information is sought have been suspected of plumbism or have had a definite history of exposure to the metal. It occurred to us that a class of first year medical students, selected from all parts of the country, would be excellent material for such a study. Consequently, we examined blood samples from the first year medical students in the entering class of 1936. Inquiry revealed that for the most part the subjects were free from definite exposure to lead. Some 12 or so gave a history of recent but casual contact with a possible source of the metal. None of the members of the series was employed in an industry or private pursuit known to be hazardous from the standpoint of lead intoxication within the last year.

One difficulty with such a group is the great preponderance of males. In our series, for example, there were 83 males and 6 females. But a similar sex ratio might be expected from the average group of workers in industry, so that for purposes of comparison our series is not without direct value.

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Method. Spectra of blood samples were obtained with an interrupted arc. The electrodes used were carbon rods especially purified for spectrographic analyses. As an added precaution each electrode was pre-heated to white heat in an oxygen-gas flame. Rarely if ever was difficulty encountered with contaminants in the electrodes after such treatment.

Blood samples were drawn into pyrex test tubes which had been cleaned finally in pyrex glass-distilled nitric acid. The tubes were stoppered with corks covered with a good grade of waxed paper to exclude dust and prevent contamination. After the blood had clotted, small pieces of the clot were placed on the ends of the electrodes and dried with moderate heat. The residue was excited in an interrupted arc. Since 100 flashes consumed nearly all the material on the electrode, it was necessary to prepare 3 separate samples. With the flashes occurring at 80 per minute, 300 flashes gave the required exposure. A Bausch and Lomb medium quartz spectrograph with a slit width of 0.015 mm. was used. Eastman 50 plates were employed throughout and gave uniformly good results.

Since these studies were made, we have found that a more uniform coating of the electrode can be had if the blood is first whipped with a motor driven stirrer until the clot is finely divided. A complete description of the apparatus for arcing the material has been described by McMillen and Scott.[4a,b] The instrument used in the present study differs slightly from that described in the above article in that the end rather than the side of the cylindrical electrode was covered with the sample. Also the electrode was held vertical and its position changed by hand.

Measurements of the lead content of the blood samples were made on the 2833.07 Å arc line.[6] This line was selected in preference to other of the sensitive lines because of its freedom from coincident lines. A study of the spectral tables shows that the only possible coincident line for the 2833.07 Å lead line is the 2833.2 Å iridium line. However, the absence of iridium in the sample was guaranteed by the absence of the nearby 2836.4 Å line of iridium.

Estimates of the lead content of fluids may be made directly from density measurements of the photographed lead line. However, this method is subject to relatively large errors, of which the principle ones are those resulting from irregularities in the amount of the sample burned. To eliminate this source of error a method was adopted which relies on an internal standard. The density of an iron line near the 2833.07 Å lead line was used as a reference and all measurements on lead were made relative to iron. Iron was selected because it is recognized that the amount of this element in normal blood is relatively constant. In any event it does not fluctuate by factors of 10 or 100 as does lead. The reference line in these studies was the 2831.56Å iron line. It was not only conveniently close to the lead line under observation but it also had a comparable density. For normal blood the lead line was less intense than the iron but for definite cases of lead poisoning, the situation was reversed.

The factors leading to errors when line densities are taken as a measure of lead content of blood are apparent from an examination of the following relationship:

$$D_{Pb} \gamma (\log F_{Pb} + \log K_{Pb} + \log M) + \tau$$

where D is the line density, F the fraction of lead, by weight, in the sample. In the first place variables γ and τ are related only to the photographic process and may be regarded as constant when care is taken to assure uniformity in the developing process. The term involving K represents those factors which depend only upon the chemical and physical properties of the sample. The factors which pertain to the arcing process, *i. e.*, ex-

posure time and amount of material consumed, are taken care of by the expression containing M. By introducing the reference line, M can be eliminated giving the following:

$$D_{Fe} - D_{Pb} = \gamma \log F_{Fe}/F_{Pb} + \gamma \log K_{Fe}/K_{Pb}$$

Since K can be assumed to be constant from sample to sample and is kept constant by careful developing of the plates, the difference in density may be considered to be *directly proportional to the logarithm of the ratio of the lead to the iron content.*

For the estimation of the proportion of lead found in the series of human blood samples, a standard set of rabbit bloods, to which known amounts of the metal had been added, were arced. This standard series was prepared to give concentrations from 0.005 to 1.0 mg. % of lead. The mean density difference of four exposures per sample was determined. These data were obtained by measuring directly the photographic tracing from a recording microphotometer (Fig. 1). A straight line was drawn through the density differences when these were plotted against the log of the lead concentration. With the aid of this mastergraph and the density differences of the normal samples, the lead content of these was determined.

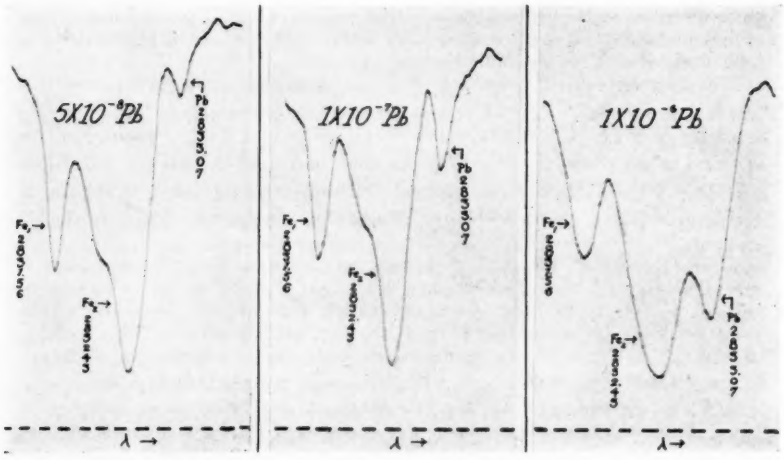

FIG. 1.—Recording microphotometer tracings of 3 leaded blood samples. A comparison of the distances of the peak for the lead line (at the extreme right of each tracing) from the dotted base line shows increasing density in the lead lines of the samples from left to right. Note the comparative equality in the level of the Feline 2831.56Å. This line was used as the internal standard for lead determinations.

Results and Discussion. In the present series, 44 blood samples failed to show traces of lead in quantities of 0.001 mg. or more per 100 cc. This figure represents the positive limit of the sensitivity of the method used without any preliminary concentration of the sample. It was felt that an extension of the procedure by attempting to concentrate the lead was disadvantageous because it not only lengthened the process but also introduced the possibility of contamination.

In the analysis of the data it was of considerable comfort to us to find about one-half (44) of our samples lead free. We interpreted this to mean that our method of blood collection was such that certainly constant, and perhaps occasional, contamination of the bloods was ruled out. It is almost axiomatic that with spectrographic studies a thorough scrutiny for all possible sources of lead contamination be given. An example of this type of contamination would be that of the solder joints in the needle used in withdrawing the sample.

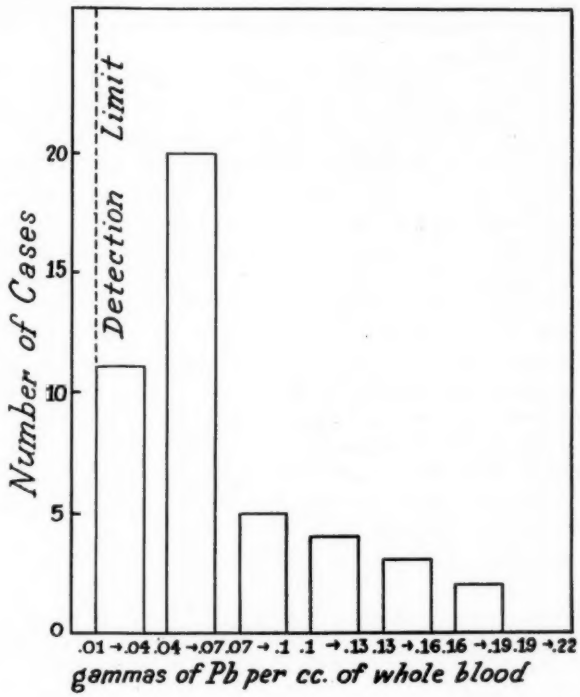

FIG. 2.—A simple graph of the distribution of lead in the 45 blood samples which showed the metal. The 44 samples which showed no lead would fall to the left of the line marked *detection limit* if the distribution graph were complete.

The next group of samples (Fig. 2) have been classed as those which contained from 0.001 to 0.009 mg. % of whole blood. In this category the bulk of the 45 lead containing bloods is to be found. Some 36 of the samples fell within this range. The modal lead content of the group was 0.004 mg. %. The distribution of this group is not symmetrical about the mean. This can be accounted for by the fact that our series had an insufficient number of cases to expect symmetrical distribution.

The remainder of the bloods, 9 in number, contain from 0.01 to 0.06 mg. % of lead. Six of these are grouped at 0.02 and 0.03 mg. %, 2 at 0.06 and 1 at 0.01 mg %. These cases with the greatest lead content of any of the series presented no symptoms, however vague, of lead poisoning. Careful questioning brought out in one case only a single clue as to the possible source of the metal. This particular person had sprayed a rose garden with lead arsenate mixture a number of times during the summer. His blood, however, contained only 0.01 mg. % of lead. The others in this group could give no suggestive answers to a large number of—to them inane—questions regarding eating, drinking, smoking and other personal habits.

The category of leaded bloods described above is of particular significance when considered in the light of the chemical findings of Litzner and Weyrauch[3] and Schmidt and Weyrauch.[5] These authors give a list of 34 cases in which the blood lead was found to range between 0.01 and 0.03 mg. %. In many of their cases the "subjektive Beschwerden" are suggestive. Even more so are their cases, 39 in number, in which from 0.03 to 0.06 mg. % of lead was found. In general, their results indicate that lead up to 0.02 mg. % may be expected in the normal and over 0.06 mg. % clinical symptoms of lead poisoning were usually found. In the present series it would seem that, with the single exception noted above, it is possible to have lead in the blood 0.0 up to 0.06 mg. % without history of lead exposure. Kehoe, Thamann and Cholak[2] report essentially the same findings for their series of 32 normal, non-industrialized Mexicans, if one discounts, as they indicate should be done, 2 cases in which the lead content of the blood was as high as 0.07 to 0.08 and 0.25 mg. %.

Spectrographic studies of pathologic amounts of lead in the blood by Blumberg and Scott[1] indicate that the pathologic range is from 0.2 to 1.0 mg. %. Our experience with abnormal amounts of lead in human blood is in complete accord with this finding. For example, a case of plumbism contracted from polluted cistern water showed 0.32 mg. % of lead.

Summary. The spectrographic methods outlined gave accurate results with the type of material studied if reasonable care was exercised. The failure to find lead in the blood in one-half of the members of the series strengthens belief in the validity of the technical procedures involved. From the findings it is reasonable to expect as much as 0.06 mg. % of lead in the blood of normal persons. While in the present series the number of females is admittedly small, no sex difference in blood lead was observed.

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THE ETIOLOGIC IMPORTANCE OF FATIGUE AND THE PROGNOSTIC SIGNIFICANCE OF MONOCYTOSIS IN NEUTROPENIA (AGRANULOCYTOSIS).

By Paul Reznikoff, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE; ASSOCIATE ATTENDING PHYSICIAN, NEW YORK HOSPITAL; ASSOCIATE VISITING PHYSICIAN, BELLEVUE HOSPITAL, NEW YORK CITY.

(From the New York Hospital and Department of Medicine, Cornell University Medical College.)

The etiologic factors responsible for malignant neutropenia or agranulocytosis have been studied intensively and much knowledge has been acquired by recent work on drug therapy and the development of the disease. The pharmacologic compounds most commonly incriminated have been amidopyrine,[16] dinitrophenol,[7] arsphenamine,[15] gold salts,[6] and recently sulphanilamide.[33] Many other medications have been mentioned. The importance of these chemicals has been variously evaluated by different authors. Kracke and Parker[13] claim that all their cases have taken drugs containing the benzene ring prior to the clinical onset of the condition. This view has received important substantiation from Plum[19] who states that no new cases of agranulocytosis have been reported in his hospital in Copenhagen from the time amidopyrine had been found to be a factor in the causation of the disease to January, 1935, whereas previously such patients were relatively common. On the other hand, Jackson[11] has shown that in 44% of 27 cases no drug has ever been used. There have been many reports based on careful investigation which substantiate this observation—that a considerable number of cases of neutropenia occur in which drug therapy is not a factor. Moreover, in a great many cases, drugs like amidopyrine have been taken for a considerable time without apparent ill effects and then suddenly the patient develops the disease.[10,11] To state that the subject has become allergic is hardly in keeping with our usual conception of allergy and is not borne out by investigation.[9,27] Moreover, if this is a peculiar type of sensitivity like an Arthus phenomenon, the search for the factors which suddenly render the resistant patient susceptible is particularly important.

Because of the apparently explosive nature of neutropenia, the high fever and the angina, an infectious etiologic agent was diligently sought. In spite of much work[5] it is generally believed now that in most cases infection is the result rather than the cause of the granulocytopenia. This has been shown by patients who had daily

blood counts for several months and in whom the neutrophil depression preceded the other symptoms and signs.[21b,22a] In a few cases the possibility of infection as one of the etiologic agents must be considered.

Menstruation is undoubtedly an important factor in this disease.[12,26,29] Many cyclical cases have been described in which this was the only etiologic condition and in which no drugs were known to have been used. One of my patients had an attack of agranulocytosis, sometimes mild and occasionally severe, every 28 days for 2 years without any use of drugs. These attacks ceased during pregnancy and after delivery never recurred. She has been free from attacks now for more than 6 years.

TABLE 1.—ETIOLOGIC FACTORS IN NEUTROPENIA.

Patient.	Sex.	Fatigue.	Drugs.	Menstruation.	Infection.	Remarks.
C. N.	♀	+	−	+	+	4 attacks; 2 infected teeth removed after fourth attack; well since; received amidopyrine during fourth attack.
G. W.	♀	+	+	−m	−	Dinitrophenol.
M. O'S.	♀	+	?	+	+	No history of drugs as cause of attack elicited; midol taken after recovery, suffered chilliness.
F. H.	♀	+	?	−m	?	Nembutal taken; difficult to determine if infection or neutropenia was primary.
L. W.	♀	?	+	−m	?	Amidopyrine; history of fatigue not determinable.
R. McC.	♂	+	+	−	?	Salvarsan; lues.
E. S.	♀	+	+	+	−	Allonal.
W. Z.	♂	+	+	−	+	Amidopyrine; clinical diagnosis: aplasia of bone-marrow or leukemia; autopsy diagnosis: chronic neutropenia.
H. H.	♂	?	+	−	+	Lues; neosalvarsan; chronic Vincent's angina; history of fatigue not determinable.
P. H.	♂	+	+	−	+	Amidopyrine, sinusitis.
G. B.	♀	+	+	−m	?	Allonal; difficult to determine if infection or neutropenia was primary.
S. W.	♀	+	?	−m	−	Roentgen ray therapy before attack; no history of drug elicited.
E. F.	♀	+	+	−m	+	Arthritis; chronic pharyngitis; amidopyrine.

m = passed menopause.

A careful study of patients' histories makes it evident that a great many cases are associated with fatigue. Sometimes the story dealt with excessive work and worry. Usually sleeplessness was present. Some of these patients took amidopyrine for this condition but many did not. In some reports it is difficult to determine whether the fatigue was not an evidence of the disease as in the chronic cases of agranulocytosis. But in many individuals long continued fatigue preceded acute attacks and in some, blood studies showed normal counts during the fatigued states which antedated the acute illness.

To determine the relative importance of the etiologic factors mentioned, 13 cases admitted to this hospital during the past 5 years were studied (Table 1).

It can be seen that fatigue previous to the onset of illness was found to be a prominent predisposing factor in 11 of the 13 patients.

In 2 cases (L. W. and H. H.) no inquiry was made as to this fact. Drugs were known to be of etiologic significance in 9 cases, amidopyrine in 6, arsphenamine in 2, and dinitrophenol in 1. In the remaining 4 cases no evidence of drug administration could be elicited. One patient (S. W.) was subjected to Roentgen ray treatment. One patient (G. N.) not only was observed through 4 attacks and known never to have taken drugs previous to the onset of the illness, but during one of her attacks received 1.62 gm. of amidopyrine as a sedative and recovered. Menstruation was a factor in 3 of the 9 female patients; 6 had passed the menopause. Infection was of possible etiologic importance in 6 patients; in 4 no history of infections could be elicited, and in 3 no previous infection was found.

An analysis of some of these cases emphasizes the importance of fatigue as a precursor to neutropenia when this factor is considered. Patient G. N. had 4 attacks. She volunteered the information that she was extremely fatigued and worried about her business before the first and third attacks. Before the fourth attack she was unable to sleep for 3 nights and was exhausted by financial and family problems. The chief therapeutic measures in her case were the removal of 2 infected teeth and the readjustment of her activities and responsibilities so that most of her worries and fatiguing duties were removed. She has had no further trouble since September, 1932. She had never taken drugs.

Patient G. W., who had taken dinitrophenol, stated that for weeks before her illness she was engaged in "hectic social life," having very little time for sleep or rest.

Patient M. O. S. took no drugs. She worked 12 hours a day at an Art Theatre, ate irregularly, and had become progressively more fatigued for a year. Her attack coincided with her menstrual period. Eleven months after her recovery she was readmitted for dilatation of her sphincter and repair of an anal fissure. She had taken Midol and in spite of having noticed a chilly sensation, her blood count showed 11,300 W.B.C. and 68% polys.

Patient F. H. complained of sleeplessness for 5 nights. The only drug she received was sodium pentobarbital after her angina was present and her throat was painted with neoarsphenamine.

Patient R. McC., who had been receiving salvarsan injections twice a week for 5 weeks, stated that his sleep was so disturbed that he was sure he averaged no more than an hour's sleep for several nights preceding his attack of agranulocytosis. "He reached a breaking point from fatigue" due to his lack of sleep, his work during the day, and studying law at night.

Patient E. S. took allonal tablets for years with no apparent ill effects. She wrote a Broadway success and came East to rehearse it. She spent 18 hours a day in intensive work, could not sleep at night and was utterly exhausted at her menstrual period which coincided with her fatal attack.

Patient W. Z. was a physician who took amidopyrine occasionally. During the 2 weeks he was working day and night and was exhausted when he developed a sore throat.

Patient P. H. had a cold and could not sleep for a few days before the onset of his illness. He was exhausted and took 2 amidopyrine tablets.

Patient G. B. was always a very poor sleeper. She had been taking allonal every night for almost 3 years. For a few weeks before her attack she had been taking care of a grandchild and was utterly exhausted.

Patient S. W. was suffering from pruritus of such intensity that she could not sleep. She had also received Roentgen ray therapy for the local condition.

Patient E. F. was an elderly lady who had many responsibilities as a business manager. For one year she had felt fatigued, had arthritis and sore throats, and took amidopyrine occasionally. One day before her acute illness she was very tired but entertained some friends until late at night.

A most illuminating illustration of the importance of fatigue in neutropenia is afforded by the case record of a physician, J. J., not included in the table, who was seen after his fourth attack. He gave no history of drugs but each attack coincided with a period when he had many sleepless nights due to a concentration of obstetrical cases. His second attack was characterized by a severe submaxillary induration which necessitated the insertion of a permanent tracheotomy tube. When seen on October 13, 1933, he stated that he was very tired due to several obstetrical cases within a week, that he had little sleep for 3 or 4 nights, that he had a few more patients to deliver, and then he would take a vacation. He was so impressed with the relation of fatigue to his attacks that he planned to give up his general practice and devote himself to some less strenuous field in medicine. His W.B.C. count was 3600 and he had 37% neutrophils. The next notice of this physician appeared in the obituary column of the *Journal of the American Medical Association* of December 9, 1933, stating that his death occurred from agranulocytosis and bronchopneumonia on November 17. This fatal fifth attack was certainly associated with fatigue and might even be considered an "obstetrical death."

A perusal of the literature indicates many cases of agranulocytosis in which fatigue, worry, and sleeplessness were sufficiently marked to call the attention of the physician to this factor. In some of these, drugs are considered the most important etiologic agent; in others no evidence of drugs is found. Some of the workers who emphasized fatigue are Scanlan,[24] Reed,[20] Briscoe,[3] Roberts and Kracke,[22b] Beck,[1] Martin,[18] Hall,[8] Suzman,[28] Walker,[30] Davis,[4] Wilson,[31] Israëls and Wilkinson,[10] Klumpp,[14] von Bonsdorff,[2] and Magee.[17]

The importance of predisposing factors in addition to or other than drugs, as exemplified by fatigue, is suggested by studies on the use of amidopyrine in a large series of cases with no change in leukocyte or granulocyte counts.[25]

Table 2 presents the relationship of prognosis to the monocyte response as seen in sequential counts. Of the 13 patients, 9 recovered and all had sustained relative and, in most cases, absolute mono-

TABLE 2.—RELATIONSHIP OF MONOCYTE RESPONSE TO PROGNOSIS IN NEUTROPENIA.

Patient.	Monocytes on sequential counts (per cent).	Termination of illness.	Remarks.
C. N.	1st attack 47 (reported)	Recovery	
	2d attack 17	Recovery	
	3d attack 15, 11, 26, 23,* 15, 11, 9	Recovery	*Distinct improvement.
	4th attack 15, 11, 26, 23,* 15, 11, 15	Recovery	*Distinct improvement.
G. W.	32, 46,* 41, 22, 13	Recovery	*Distinct improvement.
M. O'S.	28, 30,* 23, 16, 13, 7, 8	Recovery	*Distinct improvement.
F. H.	26, 20,* 10, 12, 8	Recovery	*Distinct improvement.
L. W.	0, 20 (see remarks)	Died	Intern's estimate of smear taken 5 minutes before death.
R. McC.	54, 36, 22,* 14, 14, 9	Recovery	*Distinct improvement.
E. S.	0, 9, 1	Died	
W. Z.	0, 0, 0, 6, 13, 6, 30	Died	Clinical diagnosis: aplasia of bone-marrow or leukemia; autopsy diagnosis: chronic neutropenia.
H. H.	31, 40, 53, 65, 55, 37, 10,* 18, 16, 12, 19, 10, 12	Recovery	*Distinct improvement.
P. H.	45, 66, 26,* 24, 21, 23, 21, 10, 5, 1	Recovery	*Distinct improvement.
G. B.	9, 6, 22, 15,* 18, 17, 16, 16, 14, 11, 6, 9	Recovery	*Distinct improvement.
S. W.	10, 5	Died	Roentgen ray therapy before attack.
E. F.	1, 2, 5, 3, 3, 2, 8, 10, 15, 11,* 10, 16, 18, 12, 9, 7, 10, 8, 12	Recovery	*Distinct improvement.

cytosis. Moreover, in many of the patients an increase of monocytes preceded the return of neutrophils, the rise in leukocyte count, the drop of temperature or symptomatic improvement. Of the 4 fatal cases, 2 showed a progressive decrease in monocytes and 1 was reported to have had an increase from 0 to 20% just before death as judged by a house officer's estimate of a smear taken 5 minutes before death. The fourth patient had an atypical case diagnosed clinically as aplasia of the bone marrow or acute leukemia and chronic neutropenia at autopsy. Two days before death a count of 30% monocytes was reported. The patients who recovered had monocyte peaks ranging from 17 to 66% and in all cases the monocytosis was sustained for several days.

The importance of monocyte increase as a favorable prognostic sign has been shown previously in infections[21] and in neutropenia in particular by Rosenthal and Abel.[23] Wolff's[32] case is significant. A child was almost moribund 17 days after the onset of illness. Then the monocyte count rose to 28% and then to 57% with rapid recovery following. Briscoe's[3] patient illustrates the rise of mono-

cytes before return of neutrophils in a favorable case. In spite of occasional reports like one of Hall's,[8b] in which a fatal outcome resulted in spite of a monocyte count of 30% and subsequently of 45% it is generally found that monocytosis points to recovery.

Comment. In a disease like malignant neutropenia it is difficult to assess the relative importance of each etiologic factor in every case. Certainly drugs like amidopyrine merit careful consideration. And still individuals do not take such a medication when they are perfectly normal. Moreover, even those "sensitive" subjects who are given this analgesic experimentally and show a depression of neutrophils rarely develop the characteristic signs and symptoms of the condition. They may present mild evidences of malaise but it is unusual to encounter severe illness following such experiments in these persons who were in good condition when the drug was administered. From a practical standpoint it seems desirable to eliminate or modify all factors which may be of etiologic significance. To avoid a recurrence all patients who have recovered should be cautioned (*a*) to shun drugs known to depress the neutrophils; (*b*) to remove foci of infection if possible; (*c*) to reduce activities just before and during the menstrual period; and (*d*) to obtain adequate sleep and, as far as possible, guard against fatigue. The patients who have followed these rules have had no recurrences. The few patients who could not carry out all these suggestions found adequate sleep the most important single factor in their general improvement.

Conclusions. 1. Four factors were found to be of importance in causing neutropenia in 13 patients. These were (*a*) fatigue, (*b*) drugs, (*c*) menstruation, (*d*) infection.

2. In the cases reported in this study fatigue due to excessive work, lack of sleep, and worry was more frequently encountered than any of the other etiologic conditions.

3. Monocytosis is an evidence of good prognosis. To be significant it must occur early in recovery and persist.

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OPTIC ATROPHY IN PERNICIOUS ANEMIA.

By R. H. Kampmeier, M.D.,
ASSISTANT PROFESSOR OF MEDICINE, VANDERBILT UNIVERSITY,
AND
Edgar Jones, M.D.,
INSTRUCTOR IN CLINICAL MEDICINE, VANDERBILT UNIVERSITY, NASHVILLE, TENN.

(From the Department of Medicine, Vanderbilt University School of Medicine.)

Other than the pathologic changes in the spinal cord, involvement of the central nervous system is rare in primary anemia. Mental symptoms occur at times, but generally are due to a severe grade of anemia, rather than actual organic change. Barrett,[1] however, described focal cortical lesions accounting for psychotic manifestations.

Visual disturbances in primary anemia have been recognized for many years. These have been caused by retinal hemorrhages, edema of the nerve head and retina, and thrombosis of retinal artery or vein.

Optic atrophy has been mentioned by a number of authors as of rare occurrence. Most material available on the subject is contained in textbooks. Brain,[3] only, described optic atrophy as occurring not uncommonly, stating that "bilateral primary optic atrophy is observed in 5% of cases." Osler[9] states that optic neuritis is rare. Dana[5] noted optic atrophy only once. Grinker[7] believes that such lesions occasionally result from degeneration of retinal cells because of ischemia.

Unquestionably it is true that optic atrophy may occur as the result of ischemia, as is substantiated by such occurrence at times after severe hemorrhage from peptic ulcer, at postpartum and from other causes. However, the matter of interest to the present discussion is atrophy obviously not of ischemic origin, but rather most probably due to intrinsic degenerative changes. Of especial importance is the fact that this neurologic manifestation may be the presenting symptom, just as combined sclerosis may make itself manifest before clinical symptoms referable to the anemia itself.

Dereux[6] described a patient with optic atrophy and pernicious anemia whose vision did not improve after treatment with liver. He also noted that cranial nerve involvement in pernicious anemia

is very rare. Recently Cohen[4] reported 2 cases in which visual impairment was the presenting symptom. This report led Box[2] to record a similar case in the same journal some months later. Other than this we have been unable to find similar case reports in the literature.

Woods and Rowland[10] in a careful study of 201 patients with disease of the optic nerve found 11 in whom the etiology could not be established, but pernicious anemia was not mentioned among the possible causes. Jelliffe[8] in a very comprehensive treatise on the optic nerve and its disorders failed to mention pernicious anemia as a factor in his discussion.

Case Reports. CASE 1.*—O. M., a white male, aged 56, foreman of a road-grading gang, entered the Medical Out-patient Department of the University of Michigan Hospital on April 8, 1927. He complained of impaired vision, weakness, and numbness of the extremities. In July, 1926, the patient began to note impairment of his vision. He found that he made mistakes in reading numbers on a measuring tape used in road grading, and, as a result of these inaccuracies, was forced to quit work in October, 1926. The visual impairment was progressive at first, but had been stationary from October to the date of admission. It was impossible to read print at the time of entering the clinic. About January 1, 1927, the patient began to notice coldness of the feet and legs. Numbness accompanied this. The symptoms progressed so that upon admission he complained of coldness and numbness up to the waist. Within the preceding month he had noted stiffness of the knees while walking. The soles of the feet gave the impression as if he were "walking on cushions." There had been no loss of weight. Memory was good. There had been no bladder disturbance, shooting pains, girdle sensations nor difficulty in walking in the dark. Soreness of the tongue had not been noted. The appetite had been good. In the past history nothing of significance was found, except that a year before the patient had had a weak spell and had fainted, at which time a physician prescribed digitalis. Venereal disease was denied. The patient had been a moderately heavy smoker. He was a heavy drinker of spiritous liquors before prohibition, but since then he used only home-made beer.

Physical Examination. He was a large, fairly well nourished male. The hair was gray. The skin showed slight pallor. Pupils were contracted and unequal, the right being larger than the left; they did not react to light, but did react for accommodation. The edges of the tongue were slightly atrophic. The peripheral arteries were thickened and the brachial arteries were tortuous. The heart was normal in size, rate was 80, blood pressure 125 systolic and 80 diastolic. A systolic murmur was heard over the precordium. The aortic second sound was accentuated. The lungs and abdomen were negative. Liver and spleen were not palpable. Neurologic examination, checked by a neurologist, showed the presence of biceps, triceps and knee reflexes. The left tendo-Achilles reflex was absent, the right was diminished. Sense of position of the toes was present. Vibratory sense was lost over the left ankle. Ataxic gait was present, worse with the eyes closed. Fundus examination, checked by an ophthalmologist, showed pallor of both disks, the left showing unquestioned atrophy. At this point the tentative diagnosis was tabes dorsalis.

* Cases 1 and 3 were studied by one of us (R. H. K.) in the Department of Medicine, under the Directorship of Dr. J. D. Bruce, at the University of Michigan Hospital, Ann Arbor, Mich.

Laboratory Data. The urine was negative. Blood Wassermann test was negative. The spinal fluid was clear, contained 9 cells per c.mm., no globulin, and a negative Wassermann and gold sol. On April 14, 1927, the hemoglobin was 54% (Sahli), red blood cell count 1,800,000, and white cell count 5900. The differential count was: neutrophils, 57%; lymphocytes, 37%; monocytes, 2%; and eosinophils, 4%. Red cells showed slight poikilocytosis, anisocytosis, polychromatophilia and macrocytosis. Reticulocytes were present to 1%. The blood bilirubin was 1.5 mg. %. Achlorhydria was present.

Course. The patient was placed on high liver diet (500 gm. daily) on April 15, 1927. He was discharged from the hospital on June 1, 1927. He was given hydrochloric acid with the diet. The blood picture improved so that by April 26, the hemoglobin was 60% (Sahli), the red blood cells numbered 2,040,000 with 14% reticulocytes. Improvement was progressive and by July 1, 1927, the hemoglobin was 83% (Sahli) and red blood cell count 4,830,000. As the blood improved the gastro-intestinal symptoms disappeared and subjectively the numbness improved. Vision remained unchanged.

Case 2.—T. S., a white man, aged 59, entered the Out-patient Department of Vanderbilt University Hospital on May 12, 1936. His complaint was weakness which had been gradually progressive for 6 months following "influenza." A month after the onset of his weakness he noticed difficulty in reading newspaper print. This visual defect progressed until at the time of admission he could only distinguish large objects at short distances. Throughout his illness he has had more or less generalized soreness of his muscles. He said that while his legs and arms felt "dead," they were also tender to touch. His tongue had not been sore nor had he had any diarrhea. He had lost about 16 pounds during his illness, his weight at time of admission being 106 pounds. The past history was of no apparent significance except that all his teeth had been removed 3 years before, and he had obtained no dentures.

Physical Examination. The patient was found to be a small, poorly nourished man, appearing chronically ill. There was diffuse brown pigmentation of his face and arms, about the axillary folds, patches of similar pigmentation inside the right cheek. There was generalized muscle weakness. The pupils reacted normally to light and accommodation, and were equal and regular in outline. The ophthalmologist reported visual acuity of 5/200 for the right eye and 10/200 for the left eye. Though the patient was somewhat uncoöperative, the visual fields showed no apparent gross defect. The fundi were described as being pale in reflex and the optic disks pale with pronounced temporal pallor. The impression was optic atrophy of unknown etiology. The heart and lungs were not remarkable. There was slight tenderness just beneath the right costal margin, but nothing abnormal was felt there. The liver and spleen were not palpable. There was a hydrocele of the tunica vaginalis on the left. The knee and ankle jerks were absent. He walked with a wide base and showed a positive Romberg test. Vibratory and position senses were lost in both lower extremities. The abdominal, cremasteric, biceps and triceps reflexes were present but sluggish. A tentative diagnosis of tabes dorsalis was made and the patient was admitted to the hospital.

Laboratory Data. Red blood cell count was 1,350,000 with 5 gm. of hemoglobin. The white blood cell count was 2200 (neutrophils, 41%; eosinophils, 1%, lymphocytes, 43%; and monocytes, 15%). The smear was typical of pernicious anemia. Gastric analysis showed no free hydrochloric acid even after histamine. His spinal fluid was clear, showed no increase in pressure, no cells, a negative Pandy test and a negative Wassermann test with a flat colloidal mastic curve. The urine showed nothing

abnormal. Four stool specimens were negative for parasites, ova and occult blood.

Clinical Course. The patient was given 6 cc. of Lilly's concentrated liver extract intramuscularly daily for 4 days and then at decreasing intervals. From an initial level of 0.25%, the reticulocytes increased to 42% 6 days after beginning specific treatment. This was followed by a rise in red cells and hemoglobin to 3,750,000 and 11 gm. respectively, 19 days after the beginning of liver therapy, at which time he was discharged from the hospital. There was marked subjective improvement both in strength and vision. However, tests of visual acuity made approximately 3 months after the first tests showed values of 2/200 for the right eye and 10/200 for the left eye. The fundi and nerve heads appeared as on the first examination, as did the visual fields. Six months after admission to the hospital, the red blood cell count was 5,200,000 with 16.5 gm. of hemoglobin. He had been receiving liver extract regularly at weekly intervals during this time. There had been a gain of 6 pounds in weight. Newspaper headlines were now visible for the first time since the period of observation began. Ten months after admission to the hospital his visual acuity was 20/200 for the right eye and 20/200 for the left eye.

CASE 3.—N. W., a white male, aged 50, boiler-maker by occupation, entered the Medical Service of the University of Michigan Hospital on November 17, 1925. His complaints were weakness and shortness of breath, which began 6 months before. Because of weakness he gave up work for 3 months, then regaining strength, he again worked until 12 days before admission to the hospital. He noted a burning sensation of the tongue. Numbness and coldness of the feet were present at the onset of the illness. These symptoms improved, but the abnormal sensation was felt in other parts of the body. Later the feet became so tender he could not walk. Ataxia developed. Vision had become progressively worse since the onset of the present illness. There was nothing of significance in the past history. The patient did not use alcohol. The wife and 6 children were living and well.

Physical Examination. Only important points in the examination are mentioned. The patient presented a marked pallor with a yellow tint. Pupils were irregular and failed to react to light. The tongue showed atrophy of the papillæ. Deep reflexes were normal. The ophthalmologist reported bilateral optic atrophy.

Laboratory Data. Blood Wassermann test was negative. On admission to the ward, the blood showed a hemoglobin of 22% (Sahli), red blood cell count of 820,000 and white cell count of 3200. The red cells presented anisocytosis and poikilocytosis.

Clinical Course. During the course in the hospital, the patient received 10 blood transfusions. At no time did the hemoglobin or red cell count rise above 31% and 2,600,000 respectively. The blood values steadily decreased from the high point. Edema, hydrothorax and ascites developed, and the patient died 4 months after admission. Permission for autopsy was not obtained.

Comment. Three cases of primary anemia have been presented in which visual impairment was prominent. In the first case, it was the presenting symptom and only symptom for 6 months, and on the first examination the patient had an anemia not severe enough to account for the changes on the basis of ischemia. Because he was seen during the prohibition era when methyl alcohol poisoning was not uncommon, this phase of the history was carefully considered.

In the second case, the visual disturbance appeared early among

the symptoms and again at a time when the degree of anemia could not account for the optic lesion.

The third case was included in this report because optic atrophy was present in a patient who undoubtedly had primary anemia. Study was incomplete in that no spinal fluid examination was included. This patient had an anemia of such grade upon admission that question might arise as to the part played by ischemia in the production of optic atrophy. However, visual symptoms had steadily progressed from the onset of symptoms and during a probable remission.

Especially worthy of emphasis are the diagnostic aspects of such cases. In the first 2 cases the early tentative diagnosis was tabes dorsalis.

Discussion. Since visual disturbance is not generally included as one of the usual symptoms of pernicious anemia, it seems worth while to call attention to this possibility. Especially is this of value since if such a condition is considered, treatment instituted sufficiently early may stop the progressive degeneration. Further, it brings out the fact that clinicians must be aware constantly of unusual possibilities, since the diagnosis of tabes dorsalis was initially made in the first 2 of the reported cases, because of attendant findings in addition to optic nerve changes.

The incidence of optic atrophy in cases of pernicious anemia may be gauged to some degree by analysis of case groups. During an 11-year period at Vanderbilt University Hospital, there were 69 cases of pernicious anemia. Of these, 74% were found to have symptoms or signs of central nervous system involvement. In a 5-year period preceding the admission of Case 1, 164 acceptable cases of pernicious anemia were admitted to the University of Michigan Hospital. Fifty-five per cent of these patients presented subjective or objective evidence of central nervous system changes. During the admission of the total of 233 cases to their respective hospitals there were 3 patients who suffered from optic atrophy.

As noted above, optic atrophy is occasionally known to follow severe sudden hemorrhage. It has been said that ischemia may account for optic nerve changes in pernicious anemia, but it seems to us that this belief is open to question. The sudden depletion of blood seems to be of more importance in optic atrophy due to hemorrhage than the degree of anemia. It is not infrequent to see patients with pernicious anemia having a hemoglobin of 4 to 5 gm. and a red blood cell count of 1,000,000 or less; yet optic atrophy is certainly rare in these cases, whereas in sudden hemorrhage the hemoglobin and red cell count rarely are depressed to like degree. Patients with pernicious anemia notoriously adapt themselves well to a high degree of anemia in contrast to those with anemia, usually of less degree, from other causes.

In the patients reported in this paper, 2 had blood counts and

hemoglobin values not low enough to indicate that ischemia was the factor in their optic atrophy, and nothing in the history indicated that anemia had been more severe at any time for symptoms had been progressive. The third case, though he presented a low red blood cell count and hemoglobin content, had had visual symptoms from the onset of his complaints, which seems to indicate that optic nerve disease was progressive, independent of the degree of anemia.

Summary. 1. Three cases of pernicious anemia with optic atrophy are presented.

2. The infrequency of this complication has been discussed in light of a relatively high percentage of cases showing evidence of spinal cord disease.

3. It seems to us that optic atrophy when it occurs in pernicious anemia is an intrinsic degenerative process rather than due to ischemia itself.

4. That optic atrophy may be prominent in the clinical picture of pernicious anemia, and that it may even be the presenting symptom, is emphasized.

5. It is of interest that the tentative diagnosis of tabes dorsalis was made in 2 of the 3 cases reported.

6. The early recognition of visual disturbances on the basis of pernicious anemia is essential to the preservation and possible restoration of vision.

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THE COURSE OF HYPERTENSIVE HEART DISEASE.

In Relation to Gross Arteriosclerosis.

By Nathan Flaxman, M.D.,

INSTRUCTOR IN MEDICINE, LOYOLA UNIVERSITY MEDICAL SCHOOL, CHICAGO, ILL.

(From the Departments of Medicine, Mt. Sinai Hospital and Loyola University Medical School.)

In a previous study on the etiology of organic heart disease[6a] it was stated that arterial hypertension appeared to have no relation to gross arteriosclerosis; further, that these hypertensive patients with gross arteriosclerosis have outlived the damaging effects of their hypertension and have reached the stage where they developed

the arteriosclerosis. This arteriosclerotic-hypertensive cardiac group ranks third in importance in the etiology of organic heart disease, affecting 11% of cardiac sufferers.[6a]

Apparently the original statement on this relationship was made by Lee[7] who reported that 69% of his 53 cases of hypertension had arteriosclerosis. This view was modified by O'Hare and Walker,[9] who stated that undoubtedly many cases of essential hypertension which are said to be free from association with arteriosclerosis, in reality may have a considerable degree of sclerosis of the small vessels. In spite of the anatomic findings of arteriosclerosis in the terminal arterioles of his 72 cases, Fishberg[5] offered a different opinion. He held the view as untenable that hypertension is due to the statically increased resistance offered by the organic lesions of the arterioles and that a true generalized arteriosclerosis does not exist in association with essential hypertension, and, therefore cannot be considered the cause of the latter. He added that changes in the arterioles of a nature similar to the arteriosclerosis of essential hypertension occurs physiologically with advancing years.

In an analysis of 500 cases of arterial hypertension Nuzum and Elliott[8] found no relation between arteriosclerosis of the larger vessels and hypertension. Rosenthal,[11] after a very extensive study on atherosclerosis, stated that arterial tension as determined by the weight of the heart was an important factor in the production of atherosclerosis, *but* that atherosclerosis and hypertension are not synonymous. In 48% of his cases atherosclerosis occurred without hypertension. Bell and Clawson,[2] however, from an autopsy study of 420 cases of essential hypertension, concluded that it was incorrect to state that "arteriosclerosis has no connection with hypertension."

The present clinical study of 127 patients with gross arteriosclerosis and hypertensive heart disease was analyzed with these diverse views in mind. The average known duration of the high blood pressure was 12 years for the entire group, but varied from a known duration of 3 to 22 years. The criteria followed for the diagnosis were those suggested by the American Heart Association.[3]

The highest incidence of these combined conditions fell in the seventh decade, 61.4% (Table 1). The common decade for the

TABLE 1.—PERCENTAGE IN THE AGE GROUPS.

Ages.	Male.	Female.	Total.	%.
51 to 60	18	2	20	15.7
61 to 70	70	8	78	61.4
71 to 80	23	4	27	21.3
81 to 86	2	0	2	1.6
Totals	113 (89%)	14 (11%)	127 (100%)	100

non-arteriosclerotic hypertensives is the sixth, 49.7%, with 78.8% occurring in the 40-to-60 year period, the "hypertensive age."

Many of the arteriosclerotic patients in this study (21.3%) first learned of their high blood pressure in the sixth decade, but reached the eighth decade before the break in cardiac compensation occurred.

The duration of the disease from the onset of the first cardiac symptom, dyspnea of the persistent type most often, was estimated in the 46 known deceased patients (Table 2). The data on

TABLE 2.—DURATION OF DISEASE AFTER ONSET OF CARDIAC SYMPTOMS.

	Deceased.				Living.			
Duration.	M.	F.	T.	%.	M.	F.	T.	%.
1 day to 6 months	24	2	26	56.5	33	5	38	46.9
7 months to 1 year	6	1	7	15.1	11	0	11	13.5
2 to 5 years	8	1	9	19.6	24	2	26	32.2
6 to 10 years	2	1	3	6.5	4	1	5	6.2
11 to 20 years	0	1	1	2.3	1	0	1	1.2
Totals	40	6	46	100.0	73	8	81	100.0
	(37% deceased.)				(63% living.)			

the 81 living patients was also studied in order to compare the duration in both groups of patients. Of the deceased patients, 80.4% died within 2 years after the onset of cardiac symptoms. The percentage of patients still living who were observed within 2 years after the onset of symptoms was 76.5%, approximately the same ratio.

After the appearance of congestive heart failure the duration of life in these arteriosclerotic-hypertensives was short. Of the deceased patients, 77.0% died within 6 months after the occurrence of congestive failure (Table 3).

TABLE 3.—DURATION OF DISEASE AFTER ONSET OF CONGESTIVE HEART FAILURE.

	Deceased.				Living.			
Duration.	M.	F.	T.	%.	M.	F.	T.	%.
1 day to 6 months	30	4	34	77.0	48	6	54	67.5
7 months to 1 year	3	2	5	11.1	14	0	14	17.5
2 to 5 years	4	0	4	9.8	10	2	12	15.0
6 to 10 years	1	0	1	2.1	0	0	0	0.0
Totals	38	6	44	100.0	72	8	80	100.0

TABLE 4.—PERCENTAGE OF THE AGE GROUPS AT DEATH.

Ages.	Male.	Female.	Total.	%.
51 to 60	1	0	1	2.2
61 to 70	21	3	24	53.3
71 to 80	16	3	19	42.3
81 to 88	1	0	1	2.2
Totals	39	6	45	100.0

As to the age at death in these patients, Table 4, indicates the late age at which these patients died. There were 44.5% of the deceased over 70 at the time of death. Only 1 of the 20 patients who developed cardiac symptoms in the 51-to-60 age group died in

that same age group. When this was compared with the non-arteriosclerotic hypertensive group,[6b] it was noted that 50.5% died in the same age group (51 to 60), and 30.2% died before they were 50 years.

The common cause of death was congestive heart failure (Table 5). Coronary occlusion was frequent as an additional factor in the 127 cases (Table 6), as it occurred in 9.5% of the patients. Positive blood Kahn tests were found in 7.0% of these white patients as compared with only 3.0% in the non-arteriosclerotic hypertensive white patients.[6b]

TABLE 5.—PERCENTAGE OF CAUSES OF DEATH IN 45 CASES.

Causes of death.	M.	F.	T.	%
1. Congestive heart failure	28	4	32	71.2
2. Cerebral hemorrhage	5	1	6	13.4
3. Coronary occlusion	3	0	3	6.6
4. Uremia	2	0	2	4.4
5. Spontaneous rupture of aorta	1	0	1	2.2
6. Mesenteric embolism	0	1	1	2.2
Totals	39	6	45	100.0

TABLE 6.—ADDITIONAL FACTORS IN THE 127 CASES.

Conditions.	M.	F.	T.	%.
1. Coronary occlusion	11	1*	12	9.5
2. Positive blood Kahn tests	9	0	9	7.0
3. Cerebral hemorrhage	2	2	4	3.1
4. Diabetes mellitus	2	1*	3	2.3
5. Obesity	1	1	2	1.6
6. Cardiac aneurysm	1	0	1	0.7
7. Duodenal ulcer	1	0	1	0.7
8. Femoral embolism	1	0	1	0.7

* Same patient.

Three illustrative cases have been appended to indicate several interesting features in hypertensive patients who live long enough to develop gross arteriosclerosis.

Patient 1. C. P., a 71-year-old white male laborer, was a known hypertensive with a blood pressure around 220 systolic for the past 15 years. He first learned of his elevated blood pressure in January, 1917, at the age of 55. No symptoms or signs which are related to arterial hypertension occurred until February, 1931, when he began to have frequent nose-bleeds. In December, 1931, he became markedly short of breath and this led him to seek medical attention. In January, 1932, his blood pressure was 220 systolic and 130 diastolic and it remained at that level until his death in March, 1932. On February 1, 1932, an examination revealed dulness over both lungs posteriorly with crepitant râles at the bases. The transverse diameter of the heart was 17 cm. All palpable arteries were sclerotic and hopping in character. The liver was not enlarged and no edema was noted. Death resulted from a cerebral insult. An autopsy revealed multiple areas of encephalomalacia in the cortex of the right frontal and occipital lobes, right optic thalamus and the left internal capsule. There was a marked sclerosis of the basilar cerebral arteries, the coronary arteries, and the renal arteries. The heart weighed 410 gm. and was only moderately hypertrophied. He lived 15 years with high blood pressure after it was discovered,

but undoubtedly had the hypertension a much longer period of time. Death was due to encephalomalacia and not to cardiac failure, the dyspnea notwithstanding and in spite of the involvement of the coronary arteries.

Patient 2. S. K., a 75-year-old white male, in May, 1932, complained of severe substernal pain of 5 days' durations. Dyspnea had appeared at the same time and he was very weak. He stated that he first learned he had high blood pressure in 1912 at which time it was 200, and that it stayed about the same from that time until he was 70 when it began to decline. An examination during the attack of pain revealed a blood pressure of 140 systolic and 100 diastolic. There was impaired resonance and crepitant râles over both lung bases. The transverse cardiac diameter was 21 cm. The liver was four fingers' breadth below the right costal margin and tender to palpation. There was no edema. On digitalis (grs. 3 daily) all of his symptoms disappeared and he was compensated when last seen in August, 1933, after 21 years of high blood pressure. No later trace could be found of the patient in spite of earnest effort.

Patient 3. E. S., a 67-year-old white male salesman, first learned of his high blood pressure 22 years ago when, at the insistence of his wife-to-be, he had a thorough medical check-up. For the next 18 years his blood pressure varied between 180 and 220 systolic. He took no treatment nor did he follow any self-instituted régime for reduction therapy. Both he and his wife, who is also a known hypertensive, belong to hypertensive families. Both their mothers died from congestive heart failure. Her father dropped dead on the street on his 76th birthday after having had hypertension for years. His father died of a cerebral accident, also a known hypertensive. His brother and sister have high blood pressure known for many years. Her 2 sisters are known hypertensives. All have lived the usual span of life, if not longer.

This patient had a severe epistaxis in June, 1933. About 10 days previous to the acute onset of left heart failure in March, 1937, he developed a cough which persisted and precipitated the failure. Gradually he became shorter of breath than he had ever been and was very acutely ill when examined. He had a marked pallor, with cyanosis of the nail-beds. The peripheral arteries were hard, tortuous and hopping in character. There was dulness and moist râles at both lung bases. The transverse cardiac diameter was 20 cm. The cardiac rate was 140 with frequent ventricular extrasystoles. The liver was not palpable and there was no edema. The blood pressure was 190/140. A month of rest and digitalis (grs. $2\frac{1}{2}$ daily) caused all his symptoms to subside. He continued on digitalis (℥ xxxvi daily) and returned to work with dyspnea only recurring after climbing stairs. In the latter part of May, 1937, he became obstipated due to a fecal impaction which was removed rectally under nitrous oxide anesthesia. He returned to work and continued to take his digitalis daily. Twenty-two years after he learned of his high blood pressure a persistent cough precipitated cardiac failure. His blood pressure, when last seen in October, 1937, was 180/130.

Comment. The evidence submitted tends to support the statement that these hypertensive patients were simply fortunate enough to reach the arteriosclerotic age before the symptoms and signs of concomitant hypertensive heart disease appeared. The life expectancy in essential or arterial hypertension is much longer than most physicians are accustomed to believe, Fahr[4] has stated that it averages 14 or 15 years, and that heart failure in the clinical sense does not develop in hypertension until many years have passed.

Certain impressions obtained from constant contact with hypertensive patients of all types and their personal attitude toward their high blood pressure cannot and should not be discarded lightly without further consideration. The majority of these people under discussion in this analysis took their high blood pressure as a matter of fact. Few, if any, had or had had any of the symptoms so many of the hypertensives are prone to complain of in the pre-cardiac stage. Headaches, tinnitus, dizziness, "heart-burn," and constipation were not more common than among the average group of non-hypertensive patients. The psychic factor did not enter into their attitude toward their ailment. This is most important in patients with high blood pressure. Pal[10] said, "The majority of patients with hypertonicity (hypertension) have—as long as they know nothing about their illness—no, or only slight, subjective symptoms. As soon as they learn that their condition is not normal, they feel sick, complain of their troubles and seek to find complaints. They are sick nervously, and should be treated accordingly."

Ayman[1] has repeatedly emphasized this factor in the hypertensive patient. The patients in this study gave little or no heed to their high blood pressure, as evidenced by the fact they underwent no strict dietetic or medicinal reduction therapy at any time. Many of them had a distinct apathy on the subject, which at first seemed hardly possible, and this may have aided them greatly in living longer.

Of the 81 living patients 38.4% were alive 2 to 10 years after the onset of cardiac symptoms. There was a long interval between the onset of cardiac symptoms and the occurrence of congestive heart failure; but once congestive failure appeared the duration of life was short, as 77% of the 44 deceased patients lived less than 6 months after the final stage appeared (Table 3). The longer the appearance of congestive heart failure could be delayed after the onset of cardiac symptoms, the longer the patient lived. Even in such elderly patients this was accomplished with the use of digitalis and a marked decrease in activity. Over 70% of the deceased died of congestive heart failure, and this was the main factor to be delayed or controlled as well and for as long a period as possible. Even if coronary occlusion occurred, as it did in 15 (11.8%) of the 127 patients, the prognosis was good as only 3 (20%) of the 15 died as the direct result of the occlusion.

These patients had long periods free from cardiac symptoms after they learned of their high blood pressure. They also had a comparatively longer period of freedom from congestive heart failure after the appearance of cardiac symptoms. Once the failure appeared the duration of life was short, less than 6 months usually, and this final stage was not greatly extended with the use of absolute bed-rest. Digitalis was of considerable value after the onset of cardiac symptoms as it seemed to delay the appearance of conges-

tive failure, but after the failure occurred it was of little value in relieving the signs of congestion and prolonging the life of the patient.

Summary. The course of hypertensive heart disease in 127 patients with gross arteriosclerosis, the arteriosclerotic-hypertensive group (37% known dead and 63% known living), is reported. Of these 84.3% were above 60 years, past the "hypertensive age." The known duration of the arterial hypertension was from 3 to 22 years, with an average of 12 years, but all of the patients had learned of their high blood pressure in the "hypertensive age." These patients were fortunate to live long enough to develop gross arteriosclerosis.

When congestive heart failure appeared, which was the cause of death in 71% of the deceased patients, the duration of life was short, less than 6 months in 77% of the deceased. A marked decrease in the activity of the patient and the use of digitalis (grs. 2 to 4 daily) were of considerable aid in delaying the onset of congestive heart failure and death from the time of the appearance of the cardiac symptoms.

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SPECIFIC DERMATOSES DUE TO VITAMIN A DEFICIENCY.*†

By John B. Youmans, M.D.,
and
Marvin B. Corlette, M.D.,
Nashville, Tennessee.

(From the Department of Medicine, Vanderbilt University School of Medicine.)

Specific lesions of the skin caused by a deficiency of vitamin A were first recognized and described by Frazier and Hu[5a] in China, in 1931, and independently by Loewenthal[8a] in Africa and Nicholls[9a] in India, in 1933. Similar lesions, occurring under conditions of nutritional deficiency, had been described earlier but their specific relation to vitamin A was not discovered.[1,10,14,15]

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The lesions described by Frazier and Hu[5a] consisted of dry, pigmented papules of varying size up to 5 cm. in diameter, arising at the site of the pilosebaceous follicles, principally on the extensor surfaces of the thighs and arms but extending in some cases to the shoulders, abdomen, back, buttocks and, rarely, the face and neck. The papules were conical or hemispherical and contained a central, intrafollicular plug which projected from the surface or was covered with a loosely adherent scale. When expressed the plugs left gaping cavities. The skin was generally dry, rough and wrinkled, darker than normal and often of a dull slate color. There was an absence of sweating.

The eruption described by Nicholls[9a] was similar, but in some cases the papules appeared to spread laterally producing subangular, slightly raised, flattened areas of smooth epidermis contrasting with the surrounding accentuated fissures. He named the disease phrynoderma ("toad skin") and ascribed it to vitamin A deficiency though some of his cases had dysentery and neuritis also and he thought other food deficiencies might be associated.

The papules in Loewenthal's[8a] cases presented a somewhat different appearance which he thought might be related to the degree of cleanliness or possibly to racial differences. The normal lustrous skin of the negro was dry, rough and dull grayish black. The eruption consisted of smooth-topped, black, shiny papules, about 0.5 cm. in diameter, with sharply demarcated edges and a round or polygonal shape, not coniform or obtuse as the common acne papule. The lesions were usually limited to the anterolateral surfaces of the arms and thighs with involvement of the buttocks, loins, chest and back in some cases. On the latter two surfaces they frequently merged into an acneform eruption the lesions of which differed in no way from the acne papule *except that pustulation was extremely rare*. These acneform papules were occasionally observed on the face and a similar eruption was observed by Frazier and Hu[5b] and by Nicholls. Comedones were frequent but Frazier and Hu noted that they and the acneform lesions were not found in children under 15 years of age. Pyodermic lesions were rare, especially in Loewenthal's patients, but did occur in a small number of Frazier and Hu's earlier and more severe cases.

Microscopically, the lesions were essentially identical in both Frazier and Hu's and Loewenthal's cases. The papule arose from the pilosebaceous follicle and the lumen and mouth of the follicle were dilated and plugged by a dense mass of horny, cornified epithelium arranged in more or less concentric lamellæ in which there was often a remnant of the hair. There was hyperkeratinization of the epithelium lining the follicle, hyperplasia of the adjacent epidermal cells and moderate hypertrophy of the horny layer. The cutis vera around the follicles showed a mild grade of irritative inflammatory reaction with but slight cellular infiltration. The sebaceous glands

were absent or present only in remnants. The sweat glands and their ducts showed changes similar to those seen in the pilosebaceous follicles. The acne-like papules observed by Loewenthal resembled microscopically those of acne vulgaris, *except that cellular infiltration was negligible.*

Following the original reports additional studies have been made by these authors.[5b,8b,c,9b] In addition, Sweet and K'ang[13] have reported further cases from China. From India, Aykroyd and Rajagopal[3] and Aykroyd and Krishnan[2] have described a similar eruption and Radhakrishna Rao[11] has made a histopathologic study of a number of cases with findings which are essentially identical with those described by Frazier and Hu and Loewenthal. However, those Indian writers express some doubt that the eruption is due solely to a deficiency of vitamin A. Similar papular lesions in association with keratomalacia have been observed by R. E. Wright in Madras[17] and by Giblin among the Papuan natives.[6] In 1930, E. J. Wright[16] described a keratosis of the skin in what he termed cases of "A and B avitaminosis diseases" in Sierra Leone. Finally, 1 case has been reported by Goodwin[7] in London. As yet, this manifestation of vitamin A deficiency is not familiar to most American and European physicians, probably because the more severe degrees of this deficiency are uncommon in those countries and the frequent mild cases with less fully developed eruptions pass unsuspected.

During the past 2 years we have observed a number of patients with an eruption which we believe is due to vitamin A deficiency, 20 of which have been studied in some detail. Of these we have selected 6 for this report.* So far as we are aware, they are, with the exception of Goodwin's case, the first instances in white persons to be reported and the first in this country.† In nearly all the cases there was reason to suspect an insufficiency of vitamin A. In most of these this deficiency was due simply to an inadequate diet. In a few cases the deficiency was conditioned by diseases leading to a decreased intake, an improper absorption or an increased demand for the vitamin.

A part of the patients have had the dry, horny type of eruption described by Frazier and Hu. The papules, though smaller and less extensively distributed than in many of Frazier and Hu's cases were otherwise similar, grossly and histologically. In many cases the papules were no larger than those of ordinary gooseflesh. The anterolateral surfaces of the thighs and arms were most commonly

* Two of the cases reported here were mentioned briefly in a recent article by one of us (J. Am. Med. Assn., **108**, 15, 1937).

† The 2 cases reported by Scheer and Keil[12] in this country and attributed to a deficiency of vitamin C, had lesions which were similar grossly and microscopically to the lesions of vitamin A deficiency, except for the addition of hemorrhage. As suggested by Frazier and Hu,[5b] they were probably the result of a deficiency of vitamin A, complicated by a vitamin C deficiency.

FIG. 1.—Case 1. Dry, papular, "gooseflesh" lesions on the thigh; before treatment.

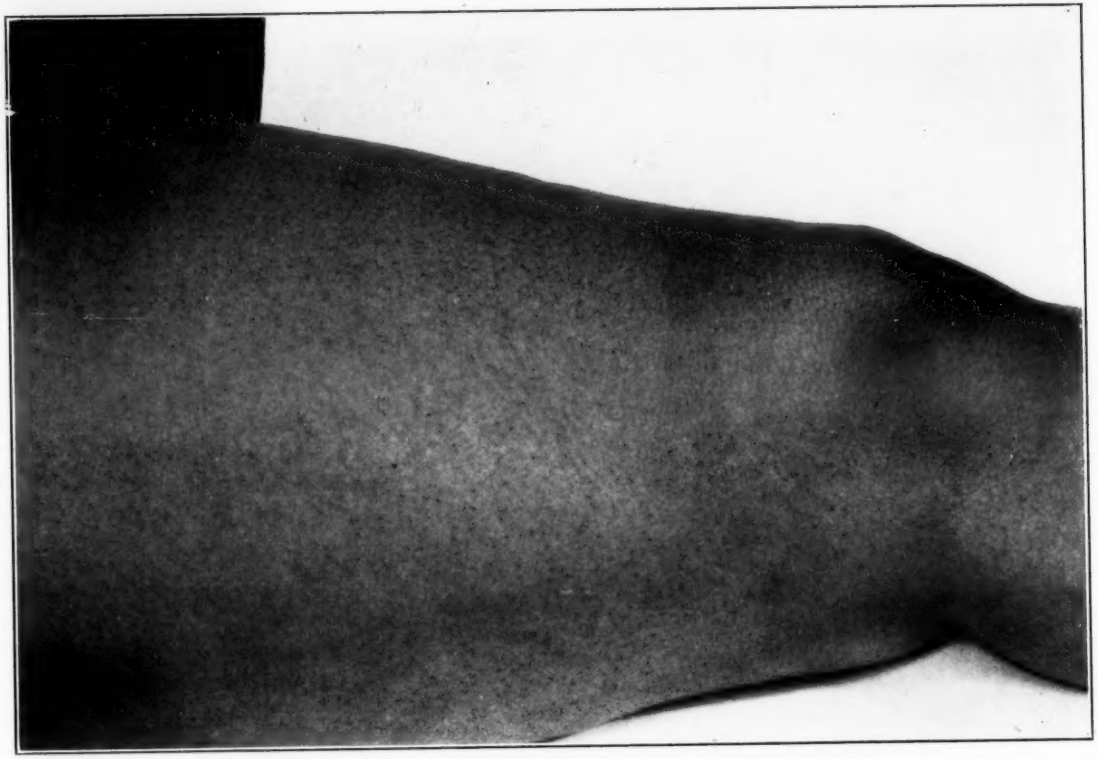

FIG. 2 —Case 1. Same region as that shown in Fig. 1; after treatment.

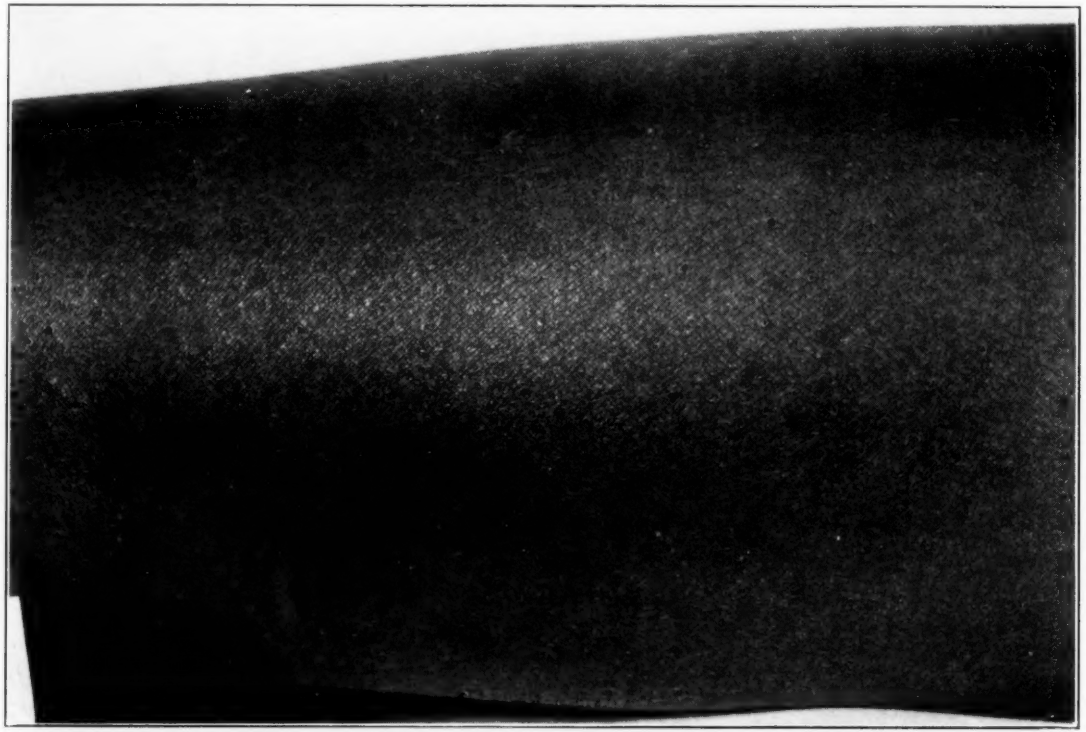

FIG 3.—Case 2. Dry, pigmented follicular papules on the thigh; before treatment.

FIG. 4.—Case 2. Section of skin from the area shown in Fig. 3, showing hyperkeratosis and a hair follicle dilated with keratinized epithelium and with hyperplastic epithelium. The sebaceous gland is absent, the sweat glands are decreased in number and small. Note the absence of cellular infiltration around the follicle and lack of cellular débris within.

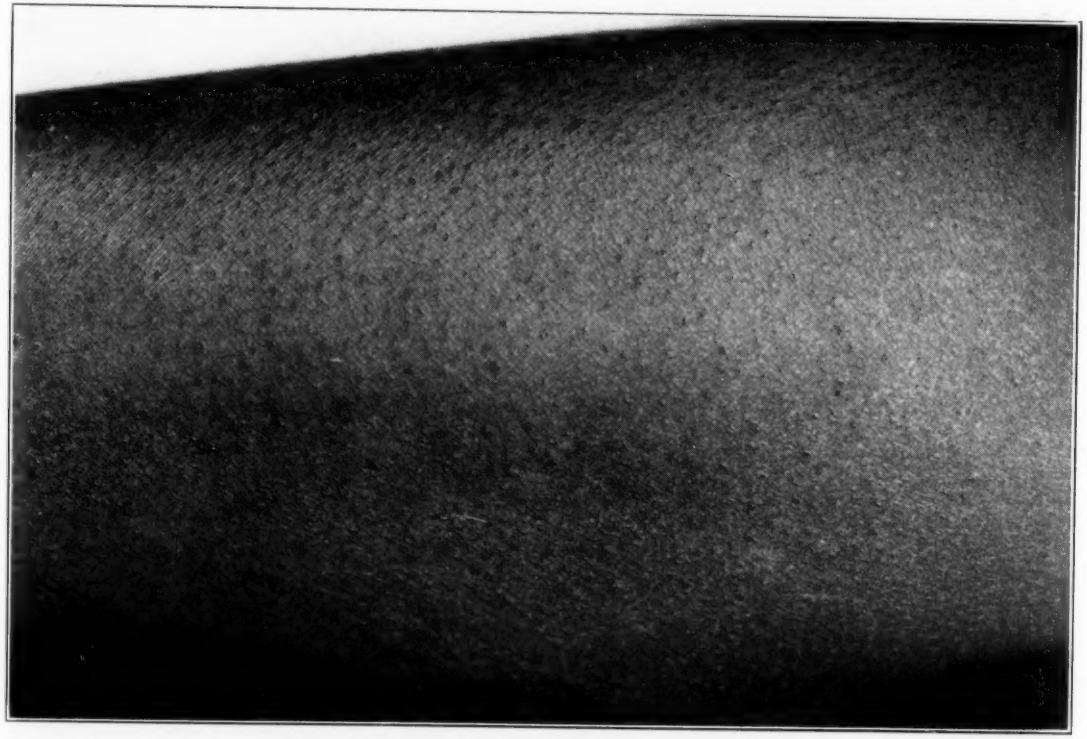

FIG. 5.—Case 2. Similar area to that of Fig. 3, showing improvement after treatment with vitamin A. There is some residual pigmentation of the site of the papules.

FIG. 6.—Case 4. The arms showing the flat, rounded, red papules. The thin whitish scale can be seen on some of the lesions. Before treatment.

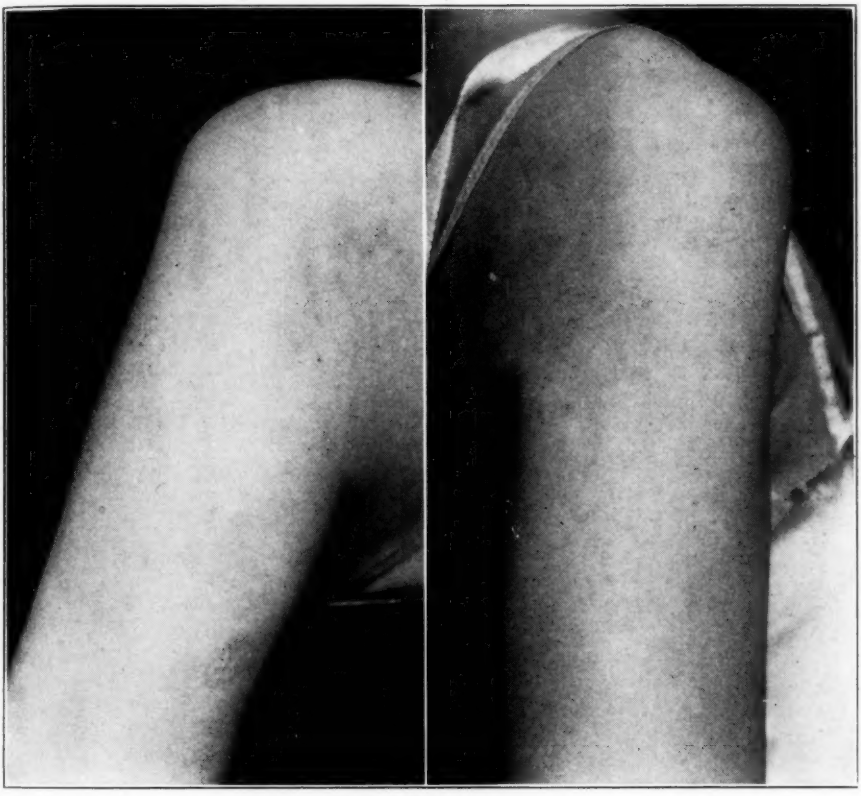

FIG. 7.—Case 4. Similar areas to those shown in Fig. 6; after treatment.

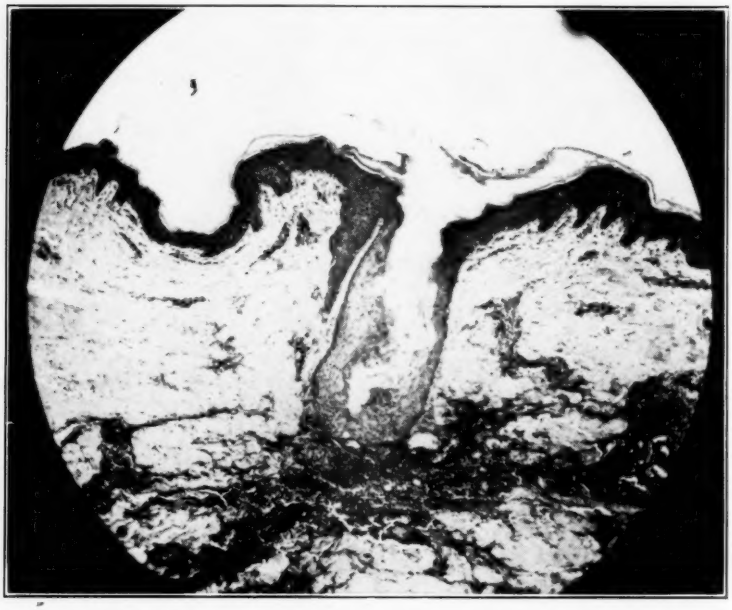

FIG. 8.—Case 5. Section of skin taken from the region of the right scapula The hair follicle is shortened and distended with keratinized epithelium which contains some cellular débris. There is a moderate infiltration of cells around the follicle.

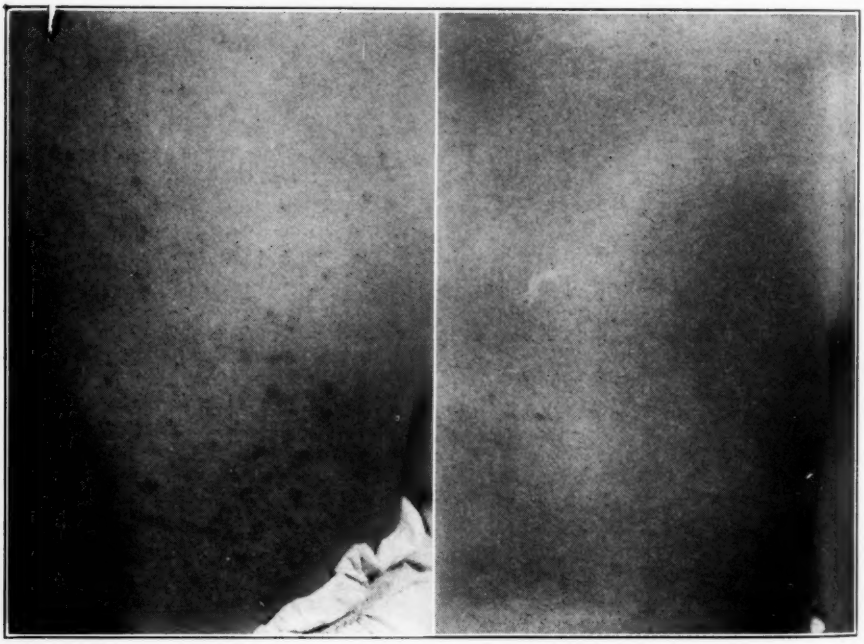

FIG. 9.—Case 6. Papular eruption on the back similar to that seen in Cases 4 and 5 Before and after treatment.

affected with the buttocks and arms next most often involved. In negroes the papules were slightly pigmented and when they disappeared under treatment left faintly pigmented scars. Pigmentation did not occur in the whites. The skin was dry and rough, especially so in the areas involved, and dull in color in the negroes. Itching was slight. Comedones were seen in some cases, presenting an incongruous appearance in the older adults, but acne-like lesions were not found in this group and infections of the skin were never observed. Bathing caused a temporary improvement in the rash making it less conspicuous but not causing it to disappear. In all the cases the eruption has disappeared or greatly improved after treatment with vitamin A. The following cases are examples of this type:

Case Reports. Case 1.—G. D., 43-year-old negress, who had attended the Out-patient Department for several years, returned, complaining of bronchitis, "pains all over," swelling of the feet, nervousness, weakness and anorexia. The food supplied by the relief agencies, although apparently reasonably well balanced, was distasteful to her and she ate little of it. On direct questioning she said she could not see to read or thread a needle and her vision was poor in the dark.

The skin was dry and rough. Over the entire lateral surface of the right thigh, part of the right buttocks and upper anterolateral aspect of the right leg there was a small papular eruption, each papule centered about a hair follicle and slightly pigmented (Fig. 1). The skin in these areas felt and looked like coarse sandpaper or gooseflesh. There were a few similar lesions on the left thigh and back. With a hand lens there appeared to be a whitish scale on the top of most of the papules. Biopsy specimens showed the characteristic changes which have been described. She was placed on cod-liver oil, 1 tablespoonful 3 times a day. Four weeks later she was much improved but it was not until about 14 weeks later that the skin had returned to normal (Fig. 2).

Case 2.—W. W., colored male, aged 29, complained of nosebleed. There was no definite history of dietary deficiency and he did not complain of a skin rash. The skin was dry and slightly scaly with a fine, horny, papular eruption over the anterolateral surfaces of the thighs and upper legs. Most of the papules were slightly pigmented (Fig. 3). Microscopic examination of a biopsy specimen showed the characteristic plugging of the pilosebaceous follicles with keratinized epithelium, absence of sebaceous glands and atrophic changes in the sweat glands (Fig. 4). He was given cod-liver oil, 1 tablespoonful 3 times a day. There was but little improvement for 12 weeks when the eruption began to regress. He was then given 16,000 international units of vitamin A daily (halibut-liver oil concentrate) and 8 weeks later the skin had returned to normal except for a residual pigmentation at the site of the lesions (Fig. 5).

Case 3.—Mrs. C. L., a white housewife, aged 48, who had formerly been treated for various gynecologic diseases returned, complaining of insomnia, "cold," cough and soreness in the chest. She could not see "half as well at night as most people." The diet had consisted mainly of beans, potatoes, turnip salad, preserved fruit and buttermilk. Over the lateral aspect of the arms and thighs the skin was dry and rough with small, dry, horny papules about the hair follicles. Histologic examination of the excised skin showed characteristic changes. She was given 12,000 units of vitamin A (halibut-liver oil concentrate) daily for 4 weeks and 25,000 units daily for 4 weeks more at the end of which time the eruption disappeared

Other patients, all of whom are white, have presented a somewhat different eruption than that just described. It has consisted solely of dull red, flat, or slightly conical, discrete papules of varying size, usually about 0.5 cm. in diameter, similar to the acneform lesions observed in some of Loewenthal's and Frazier and Hu's cases. The papules have been distributed over the anterolateral aspect of the arms, the shoulders, upper chest and back, with few, if any, on the face, abdomen or lower extremities. The individual lesions often simulate a pustule, giving the impression that by piercing or removing the whitish top a bit of pus could be obtained. When such attempts are made, however, the cap is found to be a thin, whitish scale which, when removed, leaves a raw surface and pus is not found. In some cases there are a few scattered pustules but comedones are uncommon. The skin does not appear dry or rough and itching does not occur. Microscopically, the histologic changes are similar to those of the horny type except for a slightly greater cellular reaction. The eruption has been found in adults well beyond the age of puberty and hence beyond the usual age for acne. In no case has there been a history of preëxisting acne nor scars of a previous acne eruption. In every instance the lesions have disappeared or greatly improved following the administration of vitamin A.

Case 4.—P. S., a 20-year-old white girl, was first seen in July, 1935, complaining of tiredness. The skin was clear at this time but about 3 months later she was found to have a mild diabetes and at the same time she complained of a rash. Examination showed an eruption which was diagnosed as acne vulgaris though it was thought to be atypical. There was some difficulty in following the prescribed diabetic diet, particularly in securing 5% vegetables, and the eruption becomes worse in spite of local treatments. At this time examination showed a number of scattered, dull red, rather flattened papules over the anterolateral aspect of the arms, the shoulders and upper back, with a few on the face. Among these lesions were occasional inflammatory papules which appeared to be an ordinary folliculitis (Fig. 6). A biopsy was done but the specimen was technically unsatisfactory. She was given cod-liver oil, 3 tablespoonsful daily and in 8 weeks the eruption had entirely disappeared (Fig. 7). On discontinuing the cod-liver oil the eruption returned in about 10 weeks, but disappeared after 8 more weeks' treatment with cod-liver oil.

Case 5.—Mrs. M. K., a 25-year-old housewife, whose diet appeared to be inadequate with respect to vitamin A, complained of an eruption over the upper chest, front and back. None of the lesions was pustular. Biopsy was done and the microscopic findings are shown in Fig. 8. She was given 25,000 international units of vitamin A (halibut-liver oil concentrate) daily and in 8 weeks the eruption had entirely disappeared.

Case 6.—Mrs. E. Y., a 26-year-old white housewife, came to the clinic on May 16, 1936, complaining of "funny swimming feelings." For 3 years she had had a poor appetite and ate poorly. On examination the complexion was swarthy, the skin dry. Over the back and shoulders there was a scattered small, red, papular eruption with an occasional pustule and a number of pigmented macules. The skin of the face was clear. She was continued on the same diet and given 12 cc. of cod-liver oil daily. Ten weeks later the skin was entirely normal (Fig. 9).

Discussion. There can be little doubt of the specific relation of the lesions described by Frazier and Hu and by Loewenthal to vitamin A deficiency, though some writers have discussed the possible influence of other nutritional deficiencies. In Loewenthal's cases, particularly, the evidence indicates almost conclusively that

these eruptions were due to vitamin A deficiency and vitamin A deficiency alone. As Frazier and Hu have pointed out, they are part of the widespread manifestations of this deficiency and are characteristic expressions of its effect on the epithelial tissues of the body. Nevertheless, it is possible that in some patients the eruption due to vitamin A deficiency is modified or complicated by the effect of other deficiencies, some of which also cause lesions of the skin. Multiple deficiencies are more common in practice than single deficiencies and eruptions representing combined deficiencies probably occur. The cases described by Keil and Scheer were probably of this nature. However, the essential changes due to vitamin A lack appear to be distinctive and characteristic.

In our patients with the horny or gooseflesh type of eruption the similarity of the lesions, grossly and histologically, to those described by Frazier and their response to treatment with vitamin A, identify them as a specific dermatosis due to vitamin A deficiency. In our other cases, the specific relation to vitamin A deficiency is perhaps less certain. Grossly, the individual lesions resemble in many, but not all respects, the acne papule, with the important exception as noted by Loewenthal and by Frazier and Hu, that pustulation is uncommon. Furthermore, the eruption has occurred in adults well past the acne age, without a history or scars of preëxisting acne and the affected areas are those less commonly involved by acne. Histologically, the lesions have differed from the other type only in a slightly greater cellular reaction. Finally, the eruption has disappeared following the administration of vitamin A. For these reasons, we believe the eruption is specifically related to vitamin A deficiency, the differences between it and the dry, horny type possibly due to such factors as personal cleanliness.

The relation of these changes in the skin to the other manifestations of avitaminosis A is of considerable importance. Xerophthalmia and hemeralopia were present in most of Loewenthal's cases and in many of Frazier and Hu's. Cornification of the epithelium of the conjunctivæ was observed by the latter in patients with less severe lesions of the eye. In Nicholls' cases there was night blindness. In none of our cases were there changes in the epithelium of the eye, and only occasionally was there a questionable history of mild night blindness. Studies with a visual photometer in some of our subjects demonstrated an occasional mild hemeralopia. Blackfan and Wolbach[4] and others have shown that the manifestations of vitamin A lack are evident in the epithelium of many tissues and organs and that these changes vary in respect to the order of their appearance, and their severity. Although the changes in the eye and in the vision have been thought to be the earliest reliable clinical manifestations of vitamin A lack, our observations as well as those of Frazier and Hu suggest that in some instances the skin lesions may be among the first clinical evidence of the deficiency appearing

before demonstrable changes in the epithelium of the eye and before more than a mild hemeralopia detectable only by a photometer, is present. If so, these changes may constitute one of the earliest signs of vitamin A deficiency, fortunately easily recognizable.

The time required for the eruption to disappear under the influence of treatment with vitamin A is of practical importance. Improvement is seldom noted in less than 4 weeks and in many instances 12 to 14 weeks are required before the eruption has disappeared. Night blindness or difficulty in adaptation to darkness, which is also an important diagnostic sign of early vitamin A deficiency and an index of response to treatment apparently requires only the presence of an adequate supply of vitamin A and can be corrected very quickly. Resolution of the lesions in the skin, which involves a slow process of anatomic repair, takes much longer and treatment should be continued long after the visual abnormality has been corrected. The slowness of response of the eruption to treatment is also a factor which must be taken into consideration when the response to treatment is used in diagnosis.

Summary. The occurrence of dermatoses due specifically to a deficiency of vitamin A is reported together with illustrative case reports including histologic studies. Some of the cases presented the dry, horny, papular type of lesion described by Frazier and Hu, Loewenthal, and others. Other cases presented an acne-like lesion and differed in some respects from those previously described. The histologic picture and the response to treatment with vitamin A was similar in the two types of cases. The relation between these dermatoses and other expressions of vitamin A lack particularly with reference to the diagnosis of mild or early vitamin A deficiency, is discussed.

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PERIARTERITIS NODOSA.

REPORT OF CASE DIAGNOSED CLINICALLY AND CONFIRMED BY NECROPSY.

BY BENJAMIN P. SANDLER, M.D.,
CLINICAL ASSISTANT IN MEDICINE, MORRISANIA CITY HOSPITAL, NEW YORK.

PERIARTERITIS nodosa is a rare disease. About 20 cases have been diagnosed clinically since Kussmaul first described the disease in 1866. Many cases are missed. Though there has been some discussion as to the propriety of regarding it as a clinical entity, the typical microscopic lesions entitle it to be regarded at least as a pathologic entity. It has been associated with allergic states, with acute rheumatic fever, and the suggestion made that it is a form of hyperergy to some bacterial organism, but we are really in the dark as to its etiology. The disease is usually fatal and no age is exempt. If the heart and kidneys are not involved and if the disease is confined to less vital structures, complete cure is possible once the lesions have healed and there is no recurrence. When vital organs are involved, while the patient may survive the acute stage, he will eventually die of cardiac or renal failure due to the healed arteritic lesions. The average duration has been 4 to 6 months. Acute cases were sick for only several days.

Etiology. The cause is unknown. The clinical course with fever, leukocytosis, etc., suggests an infection. A bacillus, a filterable virus, syphilis, rheumatic fever, and allergy have been mentioned by various writers; but neither bacteria nor spirochetes have been demonstrated in a lesion. The disease has been found together with acute rheumatic fever with Aschoff bodies in the myocardium.[3] Allergy has been implicated by several histories of cough, hay fever, or asthma, and by associated eosinophilia. Cohen, *et al.*[1] have shown the similarity in the vascular lesions found in the histamine reaction, the ordinary allergic wheal, and in periarteritis nodosa. The lesions in the former two are reversible, whereas in periarteritis nodosa they are irreversible.

Pathology. The lesions are found in the smaller arteries. These are sometimes recognizable grossly as firm, smooth, yellowish to red nodules found along the course of the vessel, placed at intervals, varying in size from one to several millimeters. Surrounding the nodules may be hemorrhage, infarction, or degenerative changes in the area supplied. On cut section, the lesion may be recognized grossly at times. Purplish nodular lesions have been recognized in the mesentery at laparotomy. Most often the diagnosis can only be made microscopically. One sees an inflammatory lesion, acute or chronic in nature depending on the age of the lesion. In the acute stage, there is necrosis of the media with destruction of the muscle and elastic membrane in whole or in part. This may extend

to the intima and the adventitia. At the same time there is marked infiltration of all coats of the vessel wall and the perivascular tissues with neutrophils, lymphocytes, and at times many eosinophils. There is edema and fibrin exudation. Localized weakening of the wall leads to aneurysm formation. Intimal involvement leads to thrombosis. Aneurysms may rupture and produce fatal hemorrhage. Thrombosis leads to infarction. Healing is by fibrosis and absorption of exudate. The healed vessel wall shows marked thickening and narrowing of the lumen. The reduced blood supply impairs the function of the tissue supplied and thus the signs and symptoms are produced. While typical lesions are found in the medium-sized arteries, there may also be found in skeletal muscle pericapillary infiltration of neutrophils, small round cells, and eosinophils. In our case a muscle biopsy revealed an acute focal myositis with such pericapillary infiltration (Fig. 2).

Clinical Features. The general symptoms are those usually accompanying an infection, namely, irregular fever with sterile blood cultures, prostration in the acute, and weakness, cachexia, secondary anemia, in the chronic form. Fever in the acute form is high; in the chronic, it ranges from 99 to 101° F. If cardiac involvement is present, the pulse may be disproportionately high. Leukocytosis ranges from 12,000 to 50,000. Eosinophilia is said to occur in about 12% of the cases with differential percentages ranging from 4% to 77%.[2] The blood pressure is normal if the kidneys are not extensively involved, and high if they are. The hypertension may return to normal when the process in the kidneys has subsided and the patient recovers. The hypertension, since it may be of short duration, need not produce cardiac enlargement. Added to these general phenomena are the signs and symptoms due to vascular lesions in the affected organs. Any combination of organs is possible and so the clinical picture may be exceedingly bizarre. Cardiac involvement produces symptoms of coronary sclerosis; involvement of skeletal muscles causes cramp-like pains, usually worse at night; involvement of peripheral nerves produces signs and symptoms of peripheral neuritis; involvement of appendix and gall bladder produces symptoms in the respective quadrants. Kidney involvement produces the urinary findings of nephritis. Or, there may be sudden painless hematuria when an aneurysm ruptures. Perirenal hemorrhage produces pain and mass in the lumbar region. The skin manifestations are varied. Transient erythema with subcutaneous nodules may appear anywhere. Petechiæ, purpura, ecchymoses have been described. Papulovesicular lesions over bony prominences like the knuckles and elbows may occur. These become pustular and finally hemorrhagic. They were present in our case (Fig. 1). The association of such skin lesions with evidence of heart or kidney disease, or severe asthma, or with abdominal symptoms, or peripheral neuritis, or diffuse central nervous system

FIG. 1.—Vesiculohemorrhagic lesions of the hands; those on the left hand are fresher lesions. Similar lesions found over the olecrana and patellæ.

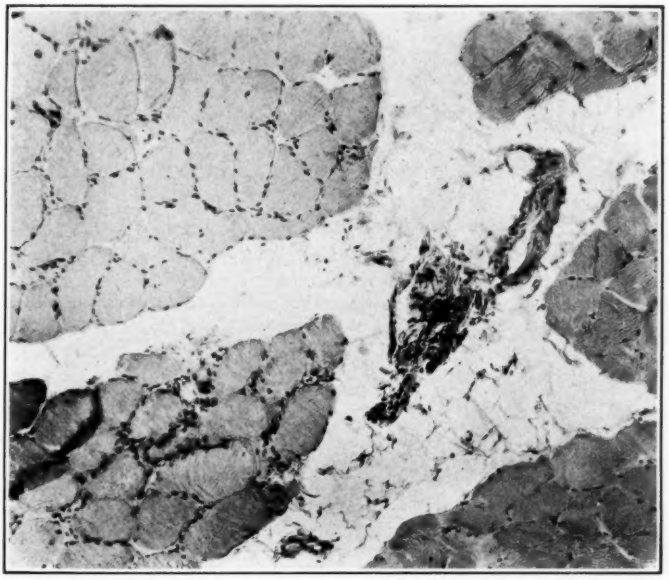

FIG. 2.—Muscle biopsy from left gastrocnemius; acute focal myositis with infiltration of neutrophils and especially eosinophils, and large mononuclear cells. There is also slight outpouring of fibrin and serum. The muscle fibers are degenerating.

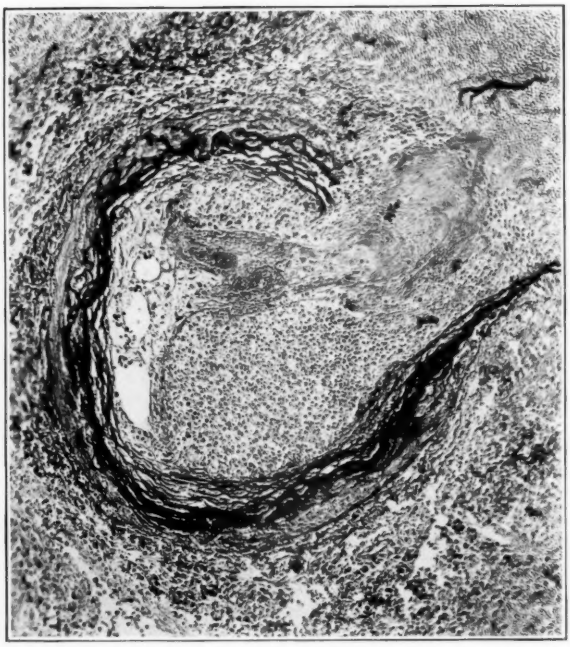

FIG. 3.—Spleen. Van Gieson elastica stain; acute panarteritis with necrosis of vessel wall and thrombosis; disruption and fragmentation of the elastic membrane

disease, should make one think of periarteritis nodosa. Edema, if generalized, may be due to cardiac or renal failure; if localized, it is probably due to involvement of the subcutaneous vessels in that area. Involvement of meningeal vessels has been reported. The spinal fluid contained numerous polymorphonuclears but no organisms.

Case Report. Patient was a white male, aged 54, born in Russia, and in the U.S.A. for 35 years. He was a tailor, married, with wife and 4 sons living and well. He had influenza in 1919. He had a mild throat-clearing cough for many years, non-productive. His present illness began in the winter of 1935 when his cough became worse. In April, 1936, he passed bright red blood in his urine. This lasted for 1 day, was painless, and never recurred. During the summer he lost 8 pounds while on vacation. In July, he had a "rash with lumps under the skin of the forehead and scalp" which lasted for 2 weeks. No physician was seen. In September, he had a severe sore throat with marked regional adenopathy. He became progressively weaker, lost his appetite, and became very constipated. About October 1st he had an attack of precordial pain radiating down the left arm but with no collapse. He was able to visit his physician who told him he had a "heart attack" and advised bed-rest. Soon pains in the forearms appeared and these lasted about 2 weeks. He remained in bed all during October, 1936. Pains in the calves came on and these were worse at night. They were described as deep and tearing, preventing sleep. This was treated as rheumatism. The patient was first seen by the author on November 19. At this time he complained of insomnia, anorexia, weakness, nervousness, constipation, cough, dryness of the nose, and severe cramps in his legs.

Physical Examination. The scalp was normal; the pupils and fundi were normal. On the inner aspect of each cheek near the opening of the parotid duct was an ulcer, the size of a nickel, and about $\frac{1}{4}$ inch deep. The regional cervical nodes were enlarged and tender. The heart was not enlarged to percussion, the sounds were of good quality and no murmurs were heard. The rate was 110 and out of proportion to a rectal temperature of 100. The blood pressure was 138/80. The lungs were normal. Abdomen was soft, non-tender, liver and spleen not felt. The testicles were small, non-tender. There was male distribution of pubic hair, and the cremasteric reflexes were present. Over the knuckles of the fingers (except thumbs) were nodular circumscribed non-tender lesions about $\frac{1}{2}$ cm. in diameter. Some were vesicular, some pustular, some hemorrhagic, similar lesions were present over the elbows and knees. The muscles of the legs were flabby, atrophic, and tender on deep pressure. The deep reflexes were present and sensation was normal. The dorsal pedis pulsations were good. Because of the buccal ulcers and the skin lesions, a blood dyscrasia was suspected. A blood count revealed: Red blood cells 3,500,000, hemoglobin 55%; no abnormal red cells; white blood cells 21,000, polymorphonuclears 88%; eosinophils 55%; neutrophils 33%; lymphocytes 12%. No abnormal white cells were found in this and subsequent counts.

The patient was then admitted to this hospital on November 23, where he remained until December 5. While there the buccal ulcers responded to treatment with mouth washes and the skin lesions disappeared without scarring. He was given a high-protein, high-carbohydrate, and high-vitamin diet. The cramps in the legs continued. He ran a low-grade fever of 99 to 101°, with persistent tachycardia of 110 to 130. There now appeared attacks of pain in the right upper quadrant and the lower abdomen. There was no nausea or vomiting. There was only slight rigidity and tenderness. The urine showed a trace of albumen; the blood Wassermann test was

negative. Agglutinins for typhoid, brucellosis, para A and B were absent. The basal metabolic rate was +1. Roentgen rays of long bones were negative and those of the chest revealed slight fibrosis of the apices. Sternal puncture revealed no abnormality in the marrow. The fragility and tourniquet tests were normal. He was discharged on December 5 with no definite diagnosis. About December 7 periarteritis nodosa was thought of and a search for subcutaneous nodules revealed several on the volar aspects of the fingers opposite the distal interphalangeal joints, very slightly tender on pressure. A nodule was removed, but on histologic examination was too necrotic to warrant any diagnosis. December 10, a subconjunctival hemorrhage appeared in the right eye with much pain and epiphora. December 15 he had a sudden severe frontal headache which lasted 20 hours. A large ecchymosis appeared in the region of the left external malleolus. December 25 the buccal ulcers recurred, December 29 he was given 500 cc. of blood, and muscle biopsy was taken from the right calf. This did not reveal the classic lesion but did reveal a focal myositis with pericapillary infiltration (Fig. 2). January 21, on getting out of bed, he felt his left arm and leg to be weak, numb, and heavy. He was unable to to stand. Examination revealed a left hemiparesis with left facial of the upper neuron type, with absent left abdominal reflex and positive left Babinski. He was mentally clear. He was rehospitalized. On January 25 a fresh ulcer appeared on the inner aspect of the left cheek with much swelling of the left side of the face. Blood examination revealed total white cells to be 14,000 with 70% neutrophils and a rare eosinophil. The patient became toxic and more drowsy; the temperature rose to 103°. It was now felt that he had a septicemia from the cellulitis of the left cheek. He died in coma on January 28. Final Clinical Diagnosis: Periarteritis nodosa; terminal septicemia following thrombophlebitis of the left angular vein.

Autopsy and Histologic Findings (Autopsy performed and sections examined by Dr. J. C. Ehrlich, Director of Laboratories, Lebanon Hospital).

Heart. The pericardial cavity contained 200 cc. of slightly turbid serous fluid. The epicardial surface was smooth. Shining through the epicardium could be seen several small punctate depressions indicating myocardial scarring. Sections of the myocardium showed extensive fibrosis despite the fact that the coronary arteries which were mildly sclerotic and narrowed, did not show any occlusion so far as they could be dissected. The right and left ventricles were slightly hypertrophied. The great vessels leading to and from the heart showed no abnormalities. The valves in both chambers were normal.

Lungs. The trachea and bronchi showed an intensely congested mucosa with actual necrotic patches. Both upper lobes of the lungs showed evidences of separated adhesions, and beneath these adhesions were subpleural anthracotic and partly calcified and tuberculosed scars. Within the right upper and middle lobes numerous miliary nodules were found on section. These nodules were firm and raised and could not be crushed. Some of them had the appearance of thickened small arterioles. A few similar nodules were found in the left lung. Otherwise the lungs were negative except for congestion.

Liver. The liver weighed 1350 gm., and was normal in shape. The capsule was smooth and showed several areas of discoloration. On section, the liver showed a striking picture, characterized by scattered irregular areas of red and gray necrosis and numerous very prominent small branches of the hepatic artery. The prominence was due to marked thickening of the vessel wall and in some cases a pin-point lumen could be recognized macroscopically. The bile passages appeared normal. The gall bladder was normal in size. The mucosa showed numerous shallow erosions. No nodules were seen along the cystic artery.

Spleen. The spleen weighed about 150 gm. and was very soft. On section, it had the soft grayish appearance of acute infectious splenitis. In addition, the cut surface showed numerous small grayish nodules similar to those seen in the liver.

Kidneys. The capsule stripped with ease. The surfaces and cut surfaces of both kidneys was studded with raised pearly-white nodules. Some of these definitely resembled arterioles that were thickened. Kidney pelves, ureters, bladder, pancreas, testes, prostate, seminal vesicles, and adrenals were all negative grossly.

Aorta. The aorta showed slight arteriosclerotic changes. Various branches of the inferior vena cava appeared normal.

Intestine. Along the course of the small mesenteric vessels were found tiny nodular thickenings through the small and large intestine.

Stomach and Esophagus. Negative.

Microscopic Findings: Heart. The myocardium shows extensive diffuse interstitial scarring, with infiltration by leukocytes, chiefly round cells, eosinophils, with occasional plasma cells. The small coronary arteries and arterioles in the myocardium are negative, except for moderate thickening of the arteriosclerotic type in some instances. Section of the mitral revealed normal architecture. Another section of myocardium reveals a periarteritic lesion in a branch of the coronary artery. This lesion is of the chronic type, with very little cellular reaction.

Lung. Sections reveal many nodular inflammatory lesions having the appearance of circumscribed areas of bronchopneumonia, with early necrosis and suppuration of the inflammatory exudate. Near one of these areas a small branch of the pulmonary artery shows a chronic arteritis. The pleura appears normal.

Liver. Numerous sections taken from various areas reveal multiple arteritic lesions, most of which are acute. These lesions are characterized by an acute panarteritis and thrombosis, sometimes with recanalization, destruction of arterial walls in varying degrees, and inflammatory exudate containing many eosinophils, as well as neutrophils, round, and plasma cells. Periarterial inflammatory exudate is likewise present. These lesions involve mostly medium-sized arteries. The parenchyma shows cloudy swelling. Elastica stains show striking disruptions in the internal and external elastic membranes, as well as large amounts of fibrinoid material in the involved vessels. The veins appear uninvolved.

Spleen. The capsule is moderately thickened with some cellular infiltrate. The pulp shows extensive inflammatory reaction, containing great numbers of neutrophils, round cells, plasma cells, and many eosinophils. Conspicuous vascular lesions consisting of acute arteritis with necrosis of muscle wall, thrombosis, and other changes described above are found in different sections.

Kidney. Sections reveal multiple miliary abscesses throughout the cortex. Several typical panarteritic lesions are also observed. There are areas of cortical parenchyma that appear normal. One of the arcuate arteries shows striking involvement. Where renal parenchyma is relatively uninvolved by vascular lesions or by infection, the glomerular and tubular elements appear relatively normal, except for severe parenchymatous degenerative changes.

Intestine. One section of intestine shows lesions of the acute and chronic variety. The mucosa of the bowel appears normal. The arteritic lesions show periarterial inflammatory changes, but the neighboring bowel wall shows no change.

Trachea. A section through one of the main bronchi shows a large arteritic lesion which is associated with rupture of the external elastic membrane and a large periarterial thrombosis.

Gall Bladder, Appendix, Testis. Sections reveal several arteritic lesions in the medium-sized branches of the cystic artery. A section of appendix shows an acute panarteritis with thrombosis of a small appendicular artery. The mucosa and wall of the appendix otherwise appear normal. Section of testis reveals fairly normal seminiferous activity along with one medium-sized artery which is the seat of an arteritis similar to that seen in other organs.

Summary. This is a case of generalized periarteritis nodosa diagnosed clinically. The disease was complicated by terminal sepsis with miliary abscesses of the lungs and kidneys. Skin nodule biopsy was inconclusive because of the extensive amount of necrosis present. A biopsy of calf muscle was also inconclusive and showed only a slight degree of focal myositis. An unusual clinical manifestation was the appearance of buccal ulcerations which may have occurred on a vascular basis. The arteritic lesions were mainly of the acute variety, a few being of the chronic variety.

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THE RELATIONSHIP OF SYDENHAM'S CHOREA TO OTHER RHEUMATIC MANIFESTATIONS.*

By Lucy Porter Sutton, M.D.,

ASSISTANT PROFESSOR OF PEDIATRICS, NEW YORK UNIVERSITY MEDICAL COLLEGE; ASSOCIATE VISITING PHYSICIAN, CHILDREN'S MEDICAL SERVICE, BELLEVUE HOSPITAL,

AND

Katharine G. Dodge, M.D.,

INSTRUCTOR IN PEDIATRICS, NEW YORK UNIVERSITY MEDICAL COLLEGE; ASSISTANT CLINICAL VISITING PHYSICIAN, BELLEVUE HOSPITAL, NEW YORK CITY.

(From the Department of Pediatrics, New York University, and the Children's Medical Service of Bellevue Hospital.)

Too many articles have been written about chorea to attempt to review the literature in this paper. We will refer only to certain papers which have appeared in the last few years which present opinions and findings somewhat at variance with the results of analyses made of patients with chorea who have been observed at Bellevue Hospital.

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For many years, although chorea minor was recognized as an entity, it was regarded as a functional nervous disorder. Finally, its clinical association with the various manifestations of rheumatic infection was noted, and for some time the probability that there is a common etiologic factor, as yet unknown, was hardly questioned. Obviously, in the absence of knowledge as to the specific etiology a definite answer cannot be given; but until then analyses of the course of the disease and its clinical manifestations may lead to tentative conclusions.

It has been interesting to review our own conception of chorea. We have studied it intensively for 10 years. At the beginning, one of the objects which we hoped to attain was some way of differentiating between the rheumatic and the non-rheumatic attacks. After following several hundred children ourselves and reviewing the records of others whose observation period began before the present study, we have come to the opinions first, that most children with chorea are rheumatic children; and, second, that if this is not true there is no clinical means at present by which it is possible to differentiate a rheumatic from a non-rheumatic attack.

The diagnosis of Sydenham's chorea is made wholly on the basis of a certain type of peculiar extraneous muscular movement. The condition should be considered a syndrome rather than a disease entity, just as we speak of acute polyarthritis as a rheumatic manifestation and not a disease in itself. Non-infectious conditions may produce the same type of movements, for instance, intracranial hemorrhage. Other infections, such as epidemic encephalitis, if the proper area of the brain is involved, may lead to choreiform movements. In such instances, which are rare compared to the frequency of Sydenham's chorea in certain communities, the history decides the etiology of the movements. All other attacks we think should be assumed to be rheumatic in origin. The reasons for this opinion will be shown.

Source of Material. The sources of our material are patients seen in the Children's Cardiac Clinic, and on the wards of the Children's Medical Service of Bellevue Hospital. For 5 years a special chorea clinic was in existence as a subdivision of the cardiac clinic, and with a special social worker to keep track of the children. The cases are still being followed, but in the regular cardiac clinic. This study is only a part of an analysis being made of 1052 rheumatic children. A total of 467 detailed records of children who had chorea and who were subsequently under observation in the clinic have been analyzed from a number of different angles. Attacks of so-called *chorea insaniens* occur entirely among an older age group than is cared for on a Children's Service Such patients are taken to the Psychiatric Division at Bellevue Hospital. Although we are given the opportunity of seeing these adults, none of them is included in this study. The clinical picture is different, with the high fever and irrationality, from that which we see in children. We have had a few 12- to 14-year-olds who were psychotic during the acute phase of the attack, but they did not fit into the chorea insaniens classification.

Precipitating Factors in Attacks of Chorea. Before presenting the data on which we base our opinion as to the relationship between chorea and other rheumatic manifestations, we will give what information we have regarding the tradition, recently revived by Gerstley[3] and Coburn,[1] of emotional disturbance as a precipitating factor in an attack of chorea. Coburn[1] says "One-half of all cases of chorea in New York may occur in individuals who are not susceptible to rheumatic fever. . . . . Their attacks were not preceded by respiratory infections, but seemed to be associated with psychic trauma."

To find the experience of our patients, 411 records of children admitted to the hospital for chorea were reviewed for any history of possible precipitating causes of the attack occurring within 2 months of the onset (Table 1). At the time the history had been taken, this point was specifically inquired into. The cases were divided into two groups, 217 seen in the first attack and 194 seen in subsequent attacks. Emotional disturbances include fright, accident, worry about school work, and so forth. The rheumatic manifestations have been divided into frank polyarthritis, in most cases occurring about 2 weeks before the onset of the chorea, subacute rheumatic manifestations such as a period of joint and muscle pains, low-grade fever, nosebleeds, and carditis. This latter small group of patients developed chorea while in the hospital for the carditis. The non-specific infections include colds, sore throats, otitis media, scarlet fever, and other acute contagious diseases.

TABLE 1.—EPISODES PRECEDING WITHIN 2 MONTHS THE ONSET OF 411 ATTACKS OF CHOREA.

Preceding episodes	First attacks, 217.				Subsequent attacks, 194.			
			No.	%			No.	%
Emotional upsets			21	9.6			18	9.2
	No.	%			No.	%		
Rheumatic episodes			30	13.8			18	9.2
Carditis	3	1.4	..	..	1	0.5		
Subacute rheumatism	12	5.5	..	..	6	3.1		
Polyarthritis	15	6.9	..	..	11	5.6		
Non-specific infections			17	7.8			9	4.8
No preceding episodes			149	68.6			149	76.8

As will be seen, among the 217 patients admitted in their first attack, 21 (9.6%) had had a recent emotional upset; 30 (13.8%) had had a recent rheumatic episode and 17 (7.8%) had had recent non-specific infections; 149 (68.6%) had had no recent previous illness or emotional upset. Among those admitted in subsequent attacks the percentage of emotional factors is almost exactly the same, while the rheumatic and non-specific infectious factors are somewhat lower. While the percentages of the total groups are too small to conclude that either psychic trauma or rheumatic manifestations are closely associated with the onset of chorea, they do

seem to show that psychic trauma is of no greater importance in precipitating attacks than is rheumatic activity, and of only slightly greater importance than non-specific infections. Kennedy[5] reminds us of the mental and nervous diseases once thought to be functional and now known to be on an organic basis, such as dementia paralytica and paralysis agitans. The fact that the etiology of a clinical syndrome is obscure is to us not justification to ascribe its origin to such a nebulous state as "psychic trauma" (Gertsley *et al.*) or to refuse to consider it as a manifestation of a diseased state. To quote Kennedy, "Only in Wonderland can we find the grin without the cat!"

Mentality of Children With Chorea. The mentality of children with chorea has received some attention, and Gerstley[3] found that 38 of the 45 children in his study had above the average intelligence. Our patients, on the basis of psychometric examinations, had the same intelligence as the general run of children seen at Bellevue Hospital, that is, they were with few exceptions normal or dull normal. Of 100 tested, the Intelligence Quotient of 83 was between 80 and 110, with the peak at 90 to 94; only 1 had the rating of over 125, and a number were far below normal. We have not found that children with chorea have any particular personality or body type. Most of our Bellevue patients, rheumatic and non-rheumatic, come from homes where economic security is absent, and where family discord is the rule, but this does not mean that these factors are necessarily a cause of chorea.

Is Chorea an Infection? Gerstley says "Chorea should not be taken as an indication of rheumatic infection without other rheumatic manifestations." Coburn says "Chorea *per se* does not suffice for the recognition of the rheumatic subject nor for the diagnosis of rheumatic activity."

If one believes that the accepted clinical evidences of infection are sure guides in the evaluation of symptoms, these statements are logical. However, adherence to this point of view would lead to improper care of patients who have an infection so subacute as to fail to produce the bodily responses which appear in the acute phase. To us, the fact that patients with chorea, in the absence of other clinical manifestations of rheumatic activity, do not present the usual evidences of infection such as fever, leukocytosis and increased erythrocyte sedimentation rate does not seem proof or even good evidence that the condition is non-infectious. One of our patients, reported in a previous article,[8a] who died accidentally during an attack of chorea, had none of the clinical evidences of infection or of heart disease, but at autopsy had acute endocarditis of the mitral valve. The erythrocyte sedimentation rate, in our experience is not an infallible index of activity. We have had patients with indubitable active carditis, without congestive failure, who have had normal rates throughout the course

of the acute illness. We feel that the erythrocyte sedimentation rate is an aid, but no more than an aid, in coming to conclusions as to rheumatic activity, and that a normal rate is not proof of the absence of active infection. We do not agree with Coburn[1] that a normal rate should be adduced as "strong evidence against the rheumatic origin of chorea." We would like to call attention to the fact that disease processes may be present for some time, as in tuberculosis or cancer before becoming clinically manifest.

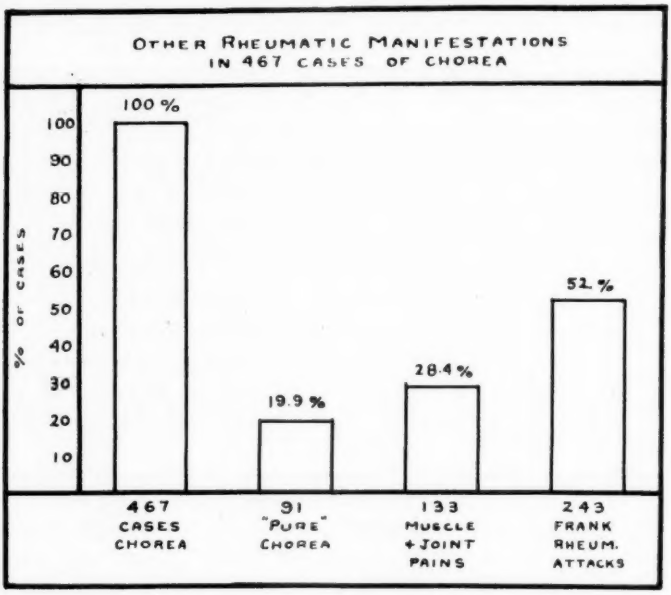

FIG. 1.—Other rheumatic manifestation in 467 cases of chorea.

The proof of an absolute relationship between Sydenham's chorea and rheumatic polyarthritis or carditis must await, as often emphasized, the finding of the cause of rheumatic fever. Until then the only way to study the question intelligently is by analyzing the course of the disease. We have approached the problem in much the same way as have other workers.

Development of Rheumatic Heart Disease in Patients With Chorea. In a group of 1052 rheumatic patients whose records are being studied, chorea was present at some time in 467 and absent in 585. Those with chorea were subdivided into those with and without other rheumatic manifestations. By "other rheumatic manifestations" we mean polyarthritis, carditis and nodules, and do not include muscle and joint pains. Although in retrospect it is frequently possible to conclude that indefinite pains were probably rheumatic in origin, it is not possible to be sure at the time the pains

occur. It is for this reason that we have not considered them among the frank manifestations of rheumatic fever, but have grouped them separately.

Figure 1 shows the incidence of other rheumatic manifestations in the 467 children who had chorea. Frank rheumatic attacks occurred in 52%, muscle and joint pains in 28.4%, while 91 (19.9%) had chorea only.

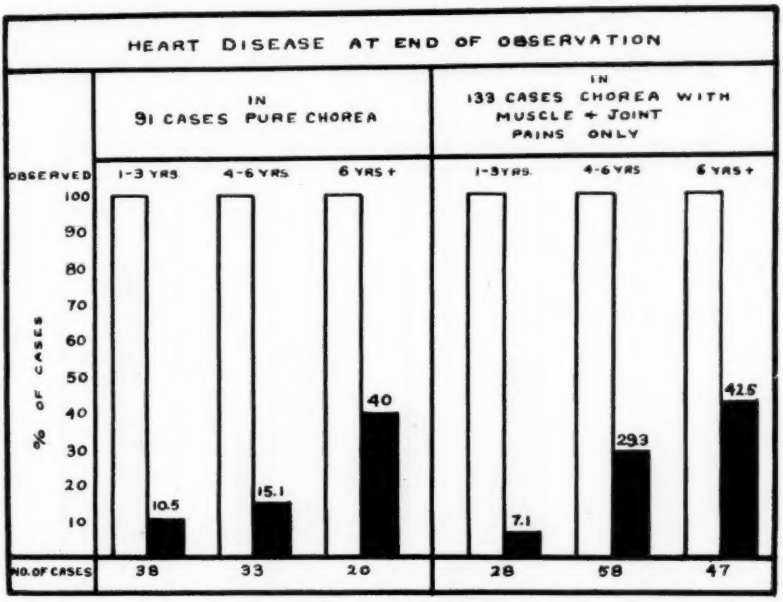

FIG. 2.—Heart disease at end of observation in 91 cases of pure chorea, 133 with chorea and muscle and joint pains.

These groups were analyzed for the incidence of organic heart disease at the end of observation. Among the 467 patients who had chorea there were 91 (19.9% of the total group) who never at any time had any other frank manifestations of rheumatic infection or muscle and joint pains. Among the 91 were 17 patients (18.6%) who had organic heart disease at the end of a mean duration of 4.8 years from the onset of the chorea. In addition, there were 133 patients who had muscle and joint pains as well as chorea, who were therefore not considered "pure" chorea. Forty of the 133 patients (30.1%) had organic heart disease at the end of observation. If these two groups are combined there were 224 (48%) of the total 567 patients who had chorea, but no other "frank" rheumatic manifestation. The incidence of heart disease in the 224 was 25.4% at the end of observation. We did not include in these groups 20 patients who had valvular disease at the time of their first

attack of chorea (10 who were otherwise pure chorea and 10 who had muscle and joint pains in addition to chorea). If these patients are included there was an incidence of organic heart disease at the end of observation of 26.7% in the "pure" chorea group, and 33.5% in those with muscle and joint pains. Figure 2 shows graphically the distribution of heart disease in these two groups (*i. e.*, chorea only, and chorea with muscle and joint pains) by years' observation, and indicates that the longer the observation period the greater the incidence of heart disease.

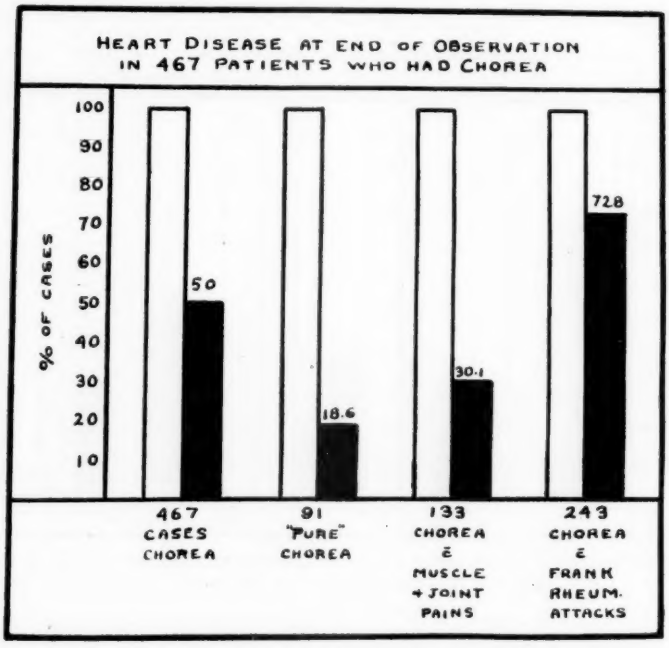

FIG. 3.—Heart disease at end of observation in 467 with chorea.

The other patients who had chorea (243) had polyarthritis, carditis or nodules either before, during or after the attacks of chorea. Of this group, 177 (72.8%) had heart disease at the end of observation. These figures are shown graphically in Figure 3. This figure may be compared with the incidence of 71.9% heart disease in the 585 rheumatic patients who never had chorea. If those with muscle and joint pains only are separated from this group there was an incidence of heart disease of 43.5% in the 108 with muscle and joint pains and of 78.4% in those with frank rheumatic manifestation (Fig. 4).

In connection with the figure for the development of heart disease in the patients with "pure" chorea (18.6% of 91 patients)

we would like to emphasize the fact that we adhered closely to the criteria for the diagnosis of heart disease laid down by the American Heart Association,[2] although we feel that in some instances the presence of a mitral systolic murmur without demonstrable enlargement means heart disease. Among these 91 patients were some who received fever therapy during the first attack of chorea. We have shown[8b] that fever therapy appears to exert some modifying effect on the development of heart disease. We feel, therefore, that our findings in regard to the development of rheumatic type heart disease in patients with "pure" chorea is under rather than over estimated.

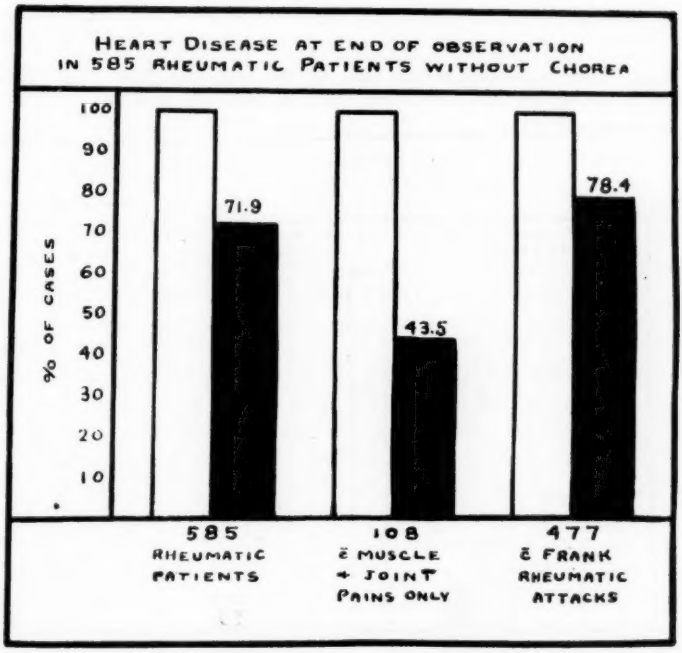

FIG. 4.—Heart disease at end of observation in 585 without chorea.

Relation of Chorea to Other Rheumatic Manifestations. We do not question the fact that chorea is not often associated with the severer forms of rheumatic infection. For instance, of 66 children admitted to Bellevue Hospital in their first attacks of rheumatic polyarthritis, 40.9% had clinical evidence of an acute carditis. To compare with these figures, 66 records of first attacks of chorea were taken at random from the files. Only 4.5% of these had active carditis. On discharge, 27.3% of the children admitted with polyarthritis had definite organic heart disease, while 13.7% of the

chorea patients had this diagnosis on discharge. These figures refer only to single first attacks.

We have analyzed the course of the disease in 124 patients who had chorea as the first rheumatic manifestation and who did not receive fever treatment; 23 were under observation 1 to 3 years; 37 for 4 to 6 years; and 64 for 7 years and longer.

TABLE 2.—THE PERCENTAGE OF SUBSEQUENT ATTACKS OF CHOREA, POLYARTHRITIS, OR OF HEART DISEASE AFTER THE FIRST ATTACK OF CHOREA.*

	1 to 3 years.	4 to 6 years.	7 to 22 years.
Number of cases	**23**	**37**	**64**
Recurrent chorea	37.5%	51.0%	76.5%
Polyarthritis	32.0%	33.0%	48.5%
Heart disease	26.0%	35.0%	53.1%
Dead of heart disease	13.0%	10.8%	7.8%

* The data are obtained from records of patients during the period of our observation. Deaths which occurred subsequently are not included. For instance, 5 other patients observed more than 6 years died, but not under our observation. If these were included, the percentage of deaths in this group would be 15.6%.

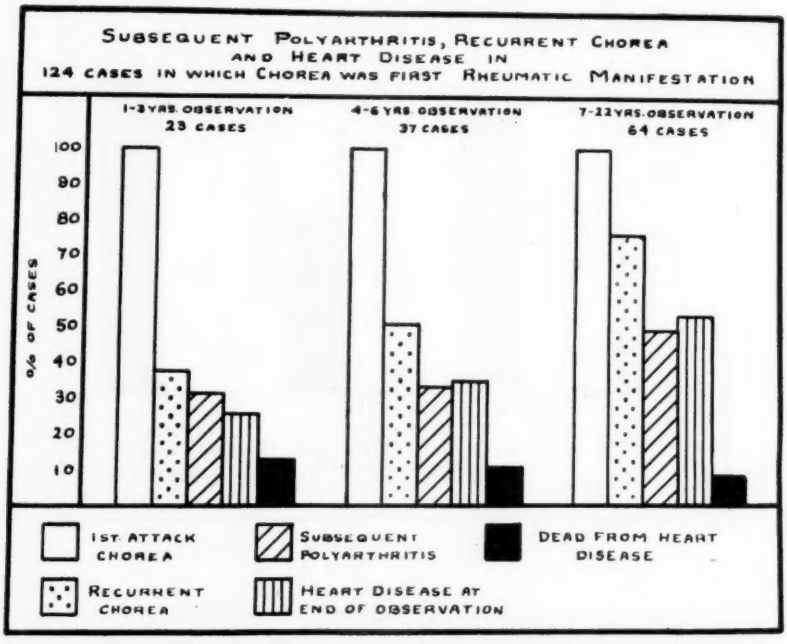

FIG. 5.—Subsequent polyarthritis, recurrent chorea and heart disease in 124 cases in which chorea was first rheumatic manifestation.

This shows that polyarthritis occurred in the subsequent course of about 50% of those who started their rheumatic career with chorea; that heart disease was present in 26% of those in the 1 to 3 year period and in 35% in the 4 to 6 year period, and 53% in those observed 7 years or longer. Figure 5 shows this graphically.

Our analysis has produced figures very similar to those of other detailed studies of chorea, with one notable exception. Jones and Bland[4] found that heart disease developed over an average observation period of 8 years in 4 of 134 patients (3%) who had chorea as their only rheumatic manifestation. They do not state, however, the exact observation periods of the patients with "pure" chorea. They use the phrase "an average observation of 8 years" for their whole group. Schwarz and Leader think, and we agree (Fig. 2), that the longer patients with "pure" chorea are observed the greater is the probability of finding that heart disease has developed. Few studies have appeared dealing with the development of heart disease in such a series of "pure" chorea. Our figure, which we feel is conservative is 18.6%; Schwarz and Leader[7] had a higher figure (52%). In our study and in Jones and Bland's, the criteria for the diagnosis of heart disease laid down by the American Heart Association were followed.[2] The difference between 3% and 18.6% obtained from similarly made analyses from presumably similar material is too great to be reconcilable. We can hardly feel that the clinical observation either on our patients or on Jones' patients were inaccurate. Since our other findings are so similar to those of the Boston investigators the material itself seems to be comparable. It would hardly be reasonable to suggest and certainly hard to prove, that chorea is less severe in Boston than in New York. It is obviously important that similar analyses should be made by other students of the disease.

Prognostic Significance of Sydenham's Chorea. One of several attitudes may be taken in evaluating the seriousness of chorea. Most important is the effect on the patient's future life and health. Our figures, and those of others, indicate the high probability of further attacks. Our figures, and those of others, indicate the probability of attacks of polyarthritis and carditis occurring in patients who have had chorea. Our figures indicate an 18.6% probability that rheumatic heart disease will develop in patients who have had chorea as the only manifestation of rheumatic infection. This is the most serious factor to be considered.

We interpret the fact that chorea is not as intimately associated with attacks of acute carditis either at the time or subsequently to mean that the rheumatic infection is not as severe in such individuals as in those who respond in terms of an attack of polyarthritis or carditis. We think it should be spoken of as one of the rheumatic manifestations, rather than a condition which "seems to play but a small rôle in the development of heart disease of the rheumatic type" (Jones and Bland) or to use the phrase which Roth[6] did in suggesting that "valvular heart disease in cases of chorea is due not to chorea but to intercurrent episodes of polyarthritis and carditis." In other words, chorea is, to us, an evidence that the patient has been attacked by the same infection which

produces rheumatic heart disease, not that chorea causes heart disease. This is more a matter of phrasing rather than a difference in fundamental conception, but accurate expression of an idea leads to clearer thinking than loose expression.

We do not take exception to Jones and Bland's opinion that an attack of chorea is not usually a serious condition in terms of survival of the attack; but our experience has been different from theirs in regard to chorea occurring during the terminal illness. They state that of 50 deaths in their series of rheumatic patients none had chorea in the last illness. We have had a number. The most recent and striking was a 7-year-old boy admitted desperately ill with pericarditis. Soon after entrance in the hospital he developed choreiform movements which progressed rapidly to a severe state. He died within 2 weeks of onset of the illness. He had had one previous attack of chorea in Bellevue Hospital at the age of 2 years and 10 months, and had been perfectly well and free from any clinical evidence either of chorea or heart disease in the *interim*. Such cases are not numerous, but do occur.

We think we are not justified in drawing definite conclusions from the evidence presented here, but that we have some basis for our opinions which are summarized below.

Summary. 1. Sydenham's chorea is not usually *per se* a serious condition.

2. Rheumatic heart disease develops in approximately 20% of patients who have had chorea as the only clinical manifestation of rheumatic infection.

3. The child who begins his rheumatic career with chorea runs a 50% chance of developing heart disease.

4. The child who begins with chorea runs a 50% chance of developing other rheumatic manifestations later, or if muscle and joint pains are included a 75% chance.

5. Emotional factors are no more important, and probably less so, in initiating an attack of chorea than preceding acute infection, including rheumatic polyarthritis.

6. Chorea should continue to be regarded not only as a manifestation, but as a major manifestation of rheumatic infection.

We wish to express our appreciation to Miss Claire Lingg, Miss Harriet Steinhilber and Miss Ethel Brown, of The Research Service of The New York Heart Association, for their invaluable help in collecting and analyzing the data presented in this paper.

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BLOOD CULTURES AFTER TONSILLECTOMY.

By Hamilton Southworth, M.D.,
ASSISTANT IN MEDICINE, PRESBYTERIAN HOSPITAL, NEW YORK CITY,
AND
Carlyle G. Flake, M.D.,
ASSOCIATE OTOLARYNGOLOGIST, CHILDREN'S HOSPITAL BOSTON, MASS.

(From the Departments of Medicine and Otolaryngology of the Johns Hopkins Hospital.)

Seifert,[13] in 1925, attempted to determine whether a significant bacteremia occurred after operation in an infected field. By taking a blood culture within 10 minutes after incision and drainage of various abscesses, he obtained from the blood stream in 45% of his 204 cases the same variety of organism that was present in the abscesses. Moreover, in 43 cases of acute appendicitis without peritonitis, he recovered the organism from the blood after appendectomy in 9 instances (21%). Similar studies of patients undergoing tonsillectomy have been made by Rubin, Epstein and Werner,[11] Schwarz and Frisch,[12] Bartlett and Pratt,[2] Wirth[15] and Fischer and Gottdenker.[5] Their results were not uniform. Thus Rubin *et al.* out of 78 tonsillectomies in children obtained not a single positive culture, though in 3 cases there was a postoperative rise of temperature to over 103°. Cultures were made in all cases with 8 cc. of blood taken preoperatively, within 30 minutes after operation, and 6 and 10 hours postoperatively, so that the series was controlled. Schwarz and Frisch[12] obtained growth in 3 cultures out of 11 taken during tonsillectomy, while cultures made 1 hour preoperatively and 7 hours postoperatively remained sterile. Bartlett and Pratt[2] report 8 positive cultures but fail to state how many cases were excluded "because of contaminants." Wirth[15], in 1932, reported not a single definite positive result in 45 cases, in each of which 6 cultures at varying time intervals were taken. He stated, however, that in a few of the cultures, organisms were obtained which on account of their non-pathogenic nature and sporadic appearance, often after many days of incubation, were considered contaminants. Finally Fischer and Gottdenker[5] in 51 cases report 16 positive cultures. Growth occurred only in 1 of the cultures taken 5 minutes postoperatively, while organisms were recovered with greatest frequency in the 2-hour postoperative cultures. Thus we find complete disagreement both as to the actual occurrence and the time of a bacteremia detectable by blood culture after tonsillectomy.

The recent excellently controlled work of O'Kell and Elliott[9] in which 60.9% of 84 cases showed a transient bacteremia immediately after dental extraction and in which the incidence of positive cultures could be directly correlated with the severity of the dental infection, aroused our interest in the question of posttonsillectomy bacteremia. Whereas O'Kell's demonstration of *S. viridans* bac-

teremia may be of etiologic significance in cases of subacute bacterial endocarditis, a streptococcal invasion, particularly of the hemolytic type, might explain the recrudescence seen occasionally in cases of glomerulonephritis and rheumatic fever that are subjected to tonsillectomy. Since the bacteremia was transient and came directly after the operative procedure in O'Kell's series and in the work of Barrington and Wright[1] on catheter fever, we decided to take our postoperative cultures as soon as possible after the operation.

Cases. Cultures were made in 22 cases in which tonsillectomy was performed by one of us (C. F.). None of the patients were very young children, the youngest being 7 years and the average 21 years of age. The patients included 4 cases of glomerulonephritis, 2 of rheumatic fever, 3 of infectious arthritis, 1 of uveitis and 8 with a definite history of recurring sore throats. All tonsillectomies were performed by semisharp dissection with scissors under gas, oxygen and ether anesthesia.

Technique. In each case a preliminary blood culture was made preoperatively just after adequate anesthesia was induced and a second culture was made within 5 minutes of the completion of the operation (usually 2 to 3 minutes after removal of mouth gag). For each culture 10 to 15 cc. of blood was withdrawn from an antecubital vein under strictly aseptic technique after preparation of the skin with iodine and alcohol. The blood was injected directly into a warmed flask of unbuffered beef infusion broth with 1% neopeptone and 0.05% dextrose and then incubated at 37° C. The flasks were observed daily for possible growth and as soon as any clouding appeared were opened and 4 to 5 drops removed with sterile pipette for streaking on a blood agar plate and for a stained smear. The original flasks were kept and observed for 21 days. Unfortunately, it was found that the blood-inoculated broth turned cloudy after 4 to 7 days even though sterile. After this had occurred, the flasks were opened and subcultured as above described every 3 to 4 days up to the 14th day and then again on the 21st day. This was done to make certain that no organism produced a transient growth under cover of the cloudiness of the broth and then died off without detection. When a subculture was positive it was immediately repeated and if the result was duplicated the original culture was considered positive. All positive results were further confirmed by direct stained smears and in none did growth fail to persist a full 7 days. Organisms obtained were identified by the standard procedures of the Biological Division. Anaërobic cultures were not attempted because organisms requiring such conditions are not usual in the tonsils and it was O'Kell's experience in his dental cases that a greater number of positive results was obtained by aërobic than by anaërobic methods. In each case the tonsils were saved and cultured. This was done by scalding them in boiling water to kill surface organisms and then by grinding them under aseptic conditions in a sterile mortar with sand and saline. Cultures were made from this material both by streaking on blood agar and by inoculating and pouring a blood agar plate. The streak and pour plates thus obtained were incubated for 48 hours so that in addition to the rapidly growing flora any minute beta hemolytic streptococci present could be identified.[6]

Results. An outline of the individual cases and the results that were obtained is shown in Table 1. Blood from 15 of the 22 cases showed no growth in either preoperative or postoperative cultures at the end of 21 days. In 3 cases, there was growth in the preoperative culture alone, but in 2 of these the growth did not appear until

TABLE 1.—ANALYSIS OF RESULTS.

Case No.	Initials.	Age.	Preoperative culture.	Postoperative culture.	Tonsil cultures.						Reason for tonsillectomy.	Max. Postop. temp.	Clin. flareup.	Length of follow-up.
					B. strep. (%).	Minute B. strep. (%).	Strep. A and G (%).	Staph. aureus (%).	H. infl. (%).	Pneu. (%).				
1	H. S.	16	0	0	..	..	35	30	25	..	Sore throat	100.2	0	7 mos.
2	M. T.	25	0	0	..	1	30	..	35	1	Infectious arthritis	100.0	0	6 mos.
3	C. P.	21	0	0	..	..	25	5	40	..	Peritonsillar abscess, history	99.4	0	5 mos.
4	M. J.	13	0	0	..	10	25	40	..	..	Rheu. ht. dis., active	99.8	0	6½ mos.
5	G. G.	32	0	0	..	5	10	20	40	..	Infectious arthritis	..	?	8 days
6	C. McC.	15	0	0	..	..	5	..	45	..	Advised by school	100.2	0	4 mos.
7	K. G.	13	*B. subtilis* on 19th day at 5th opening	0	..	..	..	..	..	..	Sore throat history	100.2	?	3 days
8	F. J.	7	0	0	20	..	..	..	..	10	Advised by school	100.2	?	2 days
9	M. P.	28	*M. tetragenus* on 15th day at 3d opening	0	5	..	40	..	..	..	Sore throat history	100.2	?	7 days
10	G. C.	20	0	0	25	..	..	50	15	..	Sore throat history	100.4	?	2 days
11	J. Z.	17	0	0	20	..	..	..	70	..	Chr. glomerulonephr.	100.6	Minimal	6 wks.
12	P. T.	14	0	*S. albus* on 23d day at 6th opening	20	..	..	30	..	20	?Rheum. ht. disease, active	101.4	0	5 mos.
13	D. F.	37	0	0	..	..	5	..	20	30	Chronic tonsillitis	99.4	0	10 wks.
14	C. M.	27	0	0	..	..	..	70	..	..	Chest cold, history	99.4	?	3 days
15	W. J.	18	0	0	30	..	30	..	..	..	Acute glomerulonephr., acute onset	104.6	Mild	6 wks.
16	M. M.	21	0	0	..	..	60	30	10	..	Infectious arthritis	99.8	?	2 days
17	W. B.	19	0	*S. aureus* on 11th day at 3d opening	..	20	..	80	..	..	Uveitis	100.0	?	7 days
18	D. T.	10	0	*H. influenzæ* on 21st day at 4th opening	70	10	..	20	..	..	Ac. glomerulonephr., acute onset	101.0	0	2 mos.
19	M. S.	41	0	0	70	..	20	..	..	..	Ac. glomerulonephr.	101.2	Definite	24 days
20	E. C.	27	Diphtheriod, 6th day, 1st opening	0	..	..	60	15	..	..	Sore throat history	99.8	?	3 days
21	J. K.	36	0	0	80	..	..	..	..	..	Sinusitis history	100.6	?	2 days
22	D. W.	9	0	*S. aureus* on 3d day at 1st opening	35	..	..	5	..	..	Sore throat history	101.0	?	1 day

late (Case 7 a *B. subtilis* on the 19th day at the 5th opening of the flask, Case 9 a *M. tetragenus* on the 15th day at the 3d opening) and it is probable that these were contaminants accidentally introduced at the previous openings of the flask. One preoperative culture (Case 20) yielded an organism with reasonable promptitude (on the 6th day at the 1st opening), but this proved to be a diphtheroid and may well have been a contaminant introduced when the blood culture was taken.

In 4 cases there was growth in the postoperative culture alone. The organisms in 3 of these (Case 12 a *S. albus* on the 23d day at the 6th opening, Case 18 a *H. influenzæ* on the 21st day at the 4th opening, and Case 17 a *S. aureus* on the 11th day at the 3d opening) may have been contaminants accidentally introduced at previous openings of the flask, though the *Hemophilus influenzæ* is such an unusual air-borne contaminant that it may have been present from the beginning and have grown out very slowly to appear on the 21st day. In the 4th postoperative culture (Case 22 a *S. aureus* on the 3d day at the 1st opening) the growth was undoubtedly primary, though the organism may of course have been a contaminant at the time of blood letting. No case gave positive results in both preoperative and postoperative cultures.

An attempt was made to correlate the type of organism obtained on postoperative blood culture with that obtained from the tonsils. Case 17 with a *S. aureus* in the blood (11th day) had 80% *S. aureus* in the tonsils, and Case 22 with a *S. aureus* in the blood (3d day) had less than 5% of this organism in the tonsils. The other 2 postoperative growths (Case 12 with a *S. albus* and Case 18 with a *H. influenzæ*) did not show these organisms on tonsil culture, and the same was true of all the preoperative positive results.

A study of the postoperative courses of the cases was made. The only patient to have a significant febrile rise after operation (Case 15 with temperature of 104.6° 24 hours postoperatively) had entirely negative blood cultures. Of the other 4 whose temperatures rose to 101° to 101.4°, 2 (Cases 18 and 22) had a positive postoperative culture. Of the 4 cases of glomerulonephritis, 3 had flareups of their disease, 1 minimal, 1 mild, and 1 quite definite with a rise in nonprotein nitrogen, but the only one with a positive culture (Case 18 with a *H. influenzæ*) was the one having no flareup. Neither of the 2 cases of rheumatic fever showed a clinical recrudescence, though in 1 (Case 12) a *S. albus* appeared in the postoperative culture on the 23d day. Of the 3 cases of rheumatoid arthritis, adequate follow up was obtained on only 1 and that patient had no flareup; in all 3 the blood culture remained sterile.

Discussion. It is to be remembered that the technique of blood culture, in which 10 to 15 cc. of blood is withdrawn, representing only a relatively minute portion of the total blood volume, is a

fairly crude method for determining slight and transient bacteremia. But interpretation must be made in the light of its results. In our cases this depends entirely on whether the few positive cultures which were obtained, represented true bacteremias or merely contaminations. This cannot be definitely determined. The technique employed necessitated such frequent subcultures (a total of 123 flask openings during the work) that the risk of contamination was unavoidable. But at least one of the organisms (*H. influenzæ*) was not a usual air-borne bacterium. The attempt to correlate the organisms found in blood cultures with those in the tonsils was successful in but 50% of the postoperative and in none of the preoperative cultures. But inasmuch as tonsillectomy is not carried out in a sterile field this confirmation could not be as rigorously demanded as in Seifert's cases in which an abscess was aseptically incised. The three factors which suggest most strongly that some of the positive results were contaminants are first, the late appearance of the growth, in several instances, of an organism which normally grows out rapidly in culture; second, the observation that the positive results were obtained in nearly as many preoperative as postoperative cases; and third, that when positive results were obtained they were never found in both cultures from the same patient. Obviously, however, the series is too small to permit one to draw valid statistical conclusions.

Since our results hinge on whether or not the positive cultures are thought due to contaminants, it is natural to consider if the disagreement between the other published reports is not due to differences in this interpretation, as well as to the more obvious differences in technique. Certainly the disagreement is a fundamental one and applies as well to cultures in other conditions. Thus Cecil, Nicholls and Stainsby[3] reported they had recovered organisms by prolonged culturing of blood from 61.5% of patients with rheumatoid arthritis, while several subsequent observers [4,7,8,14] have been unable to repeat this. Although it is generally believed that the blood stream of healthy individuals is sterile, there are several reports, such as that of Reith and Squier,[10] in which the observers claim to have obtained growth in a moderate proportion of entirely normal persons. For a solution of this controversy it would seem advisable: (1) that the technique of culturing be described in full detail in all protocols (as has been attempted above); and, (2) that all positive results be recorded as such, together with the reasons for and against considering them as contaminants. Meanwhile because of the conflicting reports in the literature and the paucity of our own results we feel that the existence of a blood-stream invasion in a significant number of cases following tonsillectomy has not been established.

It is of interest that a technique very similar to that employed here, when applied to a case of rheumatic heart disease (J. H. H.

65406) undergoing extensive dental extractions, resulted in a growth of *S. viridans* from the blood stream on two occasions. Both times growth occurred in the culture made 5 minutes after the extraction, whereas subsequent cultures and 1 preoperative culture remained sterile. This is in agreement with the results of O'Kell and Elliott.[9] It is obvious, however, that in the extraction of periapically infected teeth, as well as in the incision and drainage of abscesses, a purulent focus may be opened to the blood stream, while in the dissection of chronically infected tonsils such an occurrence would be unusual. This difference probably accounts for the divergent results in these two types of cases.

Conclusions. 1. Of 22 patients in whom tonsillectomy was performed and from whom preoperative and postoperative blood cultures were taken, 4 (18.2%) showed growth in the postoperative culture and 3 (13.6%) showed growth in the preoperative culture.

2. Whether these positive cultures represented true blood-stream invaders is doubtful in most of the cases and it is to be remarked that the preoperative growths were nearly as numerous as the postoperative ones, and that in no case was there growth both preoperatively and postoperatively in the same patient.

3. No constant relation could be made out between the clinical course and the presence or absence of a positive culture.

4. It is suggested that the discrepancy between the results of those who have already written on this subject is due to differences both in technique and in interpretation.

5. The authors feel that the evidence so far (both from their own series of cultures and those in the literature), does not establish the fact that a bacteremia occurs in any significant number of cases after tonsillectomy.

6. As possible explanation of the difference in the results following dental extraction and those after tonsillectomy, it is pointed out that in the former a purulent focus may be opened to the blood-stream while in the latter such an occurrence would be unusual.

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OXYGEN WANT AND INTRACRANIAL PRESSURE.

A PRELIMINARY REPORT.

BY J. MICHELSEN, M.D.,
RESEARCH ASSOCIATE, HARVARD UNIVERSITY,
AND
J. W. THOMPSON, M.B., CH.B.*
RESEARCH ASSISTANT, HARVARD UNIVERSITY, BOSTON, MASS.

(From the Fatigue Laboratory, Morgan Hall, Harvard University.)

THE syndrome of increased intracranial pressure is well known to the clinician. Its clinical diagnosis is reasonably certain in the presence of the following major manifestations: headache, together with projectile vomiting, disturbances of respiration and pulse rate, yawning and sighing, impairment of thought, mental dullness, and possibly unconsciousness with or without changes of the fundus oculi. Its presence in certain conditions, such as intracranial neoplasms, meningitis, intracranial hemorrhage, skull fracture, is undoubted, and it was formerly believed that the limits of its occurrence were well defined by such illnesses. More recently the view has developed that increased intracranial pressure may be present in more transitory states and thus may have a wider clinical importance than was previously believed to be the case.

The number of pathologic states leading to anoxemia is large; pneumonia, severe and acute anemia, and general intoxications as well as failure of circulation generally and locally, are the most prominent, but undoubtedly there are others which as yet have not been recognized in this light.

The following report deals with some of the symptoms produced by experimental induction of anoxemia especially in order to call attention to the appearance of the clinical syndrome typical of increased intracranial pressure as a manifestation of oxygen want.

Method. The experiments took place in a chamber and were carried out in association with D. B. Dill.[4] The subjects were members of the laboratory staff. The oxygen tension in the chamber was gradually lowered and kept so as to correspond to an altitude varying between 15,500 and 17,000 feet, the partial pressure of oxygen being lowered by addition of nitrogen. The subjects stayed in this chamber 4 to 7 hours. Data regarding the circulation, respiration and other factors were obtained once before the atmospheric O_2 tension had been reduced, and on 2 or 3 separate occasions during the experiment. The oxygen saturation of the blood of the subjects during the stay in the chamber varied in different persons between approximately 50 and 70%, whereas the atmospheric O_2 tension was reduced to the same degree for all individuals.

Almost all of our subjects who were exposed to low-oxygen pressure after approximately 2 hours complained of headaches. Headache, together with other neurologic symptoms as ataxia, muscular

* Leckie Mactier Fellow from the University of Edinburgh.

weakness, mental changes, has been described by Barcroft[2] and Haldane.[6] But we noticed that the headache resulting from the anoxic state artificially produced became much more severe immediately the subject breathed an atmosphere with a sufficient complement of oxygen to raise the arterial saturation to the normal level. This headache persisted for 2 to 6 hours, gradually diminishing during the last one or two until it completely disappeared. It was refractory to the usual analgetics such as aspirin and pyramidon. The effect of position is variable, but in most cases the headache is aggravated by lowering the head.

Also in the majority of our subjects, and mostly after the onset of the headache, repeated or even continuous yawning and sighing was observed. A dilatation of the retinal veins beginning early during the anoxic state preceding headache, yawning, and sighing has been seen by one of us (J. M.) in 3 of the subjects. The most severe—and significant—manifestations, however, have been observed on 2 other subjects, the authors.

Case J. M.—Four hours after the conclusion of the experiment, during which slight headache was felt, there appeared very severe headache of an intensity never before experienced, projectile vomiting and slow pulse. Vomiting occurred 3 times; the pulse rate was 52 to 56 beats per minute, the normal pulse rate in this individual being around 80 beats per minute.

Case J. W. T.—About 4 hours after the beginning of the experiment a note was taken by this subject in which there is the first mention of headache, "bad, splitting, parietal, frontal and around the ears." Thereafter the headache remained constant, until the full complement of oxygen was breathed at which time the headache was greatly aggravated. Five minutes after leaving the chamber the headache was agonizing and at that time projectile vomiting occurred. An excerpt from the notes of the physician who took charge of the subject after leaving the chamber reads as follows: "Heart rate slow, 40, regular. Sounds of good quality. Respirations regular, shallow, at times almost imperceptible. Artificial respiration at frequent intervals." The mental state of this subject following the anoxemia was characterized by a stuporous condition in which volition was at a minimum, although perception and memory did not seem significantly impaired. A more complete report of the mental condition of this subject will appear elsewhere.

Although in neurologic conditions headache alone often is a general sign of increased intracranial pressure and yawning and sighing a significant evidence of medullary compression, we do not as yet feel certain enough to make a general statement as to the underlying pathologic occurrences in those of our subjects who showed these symptoms. But we believe that in the presence of headache, together with projectile vomiting and slow pulse rate or even of these three symptoms combined with semiconsciousness disturbances of respiration and mental impairment as observed in the case of J. M. and J. W. T., the diagnosis of increased intracranial pressure is justified. Actual proof of the evidence of high intracranial pressure must await direct measurements both in the

cases when the clinical syndrome is complete and those where headache, yawning, sighing, and dilatation of the retinal veins appear as the only manifestations. Unfortunately, ophthalmoscopic examinations were not carried out during the illness of J. W. T. and J. M. above mentioned. Observations of the pressure by lumbar puncture would have yielded the clearest results, but some danger would have been incurred under the conditions of our experiments. One of us is now endeavoring to arrive at the same measurements indirectly by applying the ophthalmodynamometric technique introduced by Baillart,[1] Baurmann,[3] and Sobanski.[9]

Collateral evidence would tend to support the concept of there being an increase in the intracranial pressure during anoxemia. Forbes, Cobb and Fremont-Smith[5] were able to show an elevation in the intracranial pressure as a result of CO poisoning. Furthermore, it has been demonstrated by Landis[7] that the rate of capillary filtration is increased by oxygen lack. Increased capillary permeability being one of the important causes leading to swelling everywhere in the body, we are now seeking evidence showing how far an increase in the volume of the brain itself (brain swelling according to Reichardt[8]) may play a rôle in producing the increase of intracranial pressure following anoxemia. Other factors such as abnormalities of intracranial circulation, especially of the veins and disturbances in secretion and absorption of the cerebrospinal fluid, may also be involved in this problem.

Furthermore, the question arises why different individuals react to such a varying degree that some may be severely sick and endangered while others show just a few symptoms under the same circumstances. There may be some relationship between the amount of oxygen supplied to the brain tissue and the severity of the sickness during or after exposure to a low atmospheric oxygen tension. J. W. T., for instance, who showed the most severe symptoms, had the lowest oxygen saturation in his arterial blood we have observed in our subjects; on the other hand, J. M., having been very ill, although to a lesser degree, had an average saturation. But the saturation of the arterial blood is only one factor on which the oxygen tension in the brain depends. Rate of blood flow and metabolism have to be considered in any attempt to find a quantitative relationship between oxygen want and severity of the neurologic symptoms.

All these questions are not only of interest in our special field; they deserve the attention of the neurologist and neurosurgeon studying the mechanism of the increase of intracranial pressure. They claim the interest of everyone who sees the various cerebral manifestations in clinical cases of anoxemia, produced, for instance, by pneumonia. Therefore, we trust that this short communication may draw the attention of clinicians to the symptoms of increased intracranial pressure following anoxemia, so that the problem can be attacked on a broader basis.

Summary. 1. Clinical manifestations of increased intracranial pressure following exposure to low atmospheric oxygen tension are reported.

2. The response of individuals exposed to low-oxygen tension may vary from mild to severe headache, yawning and sighing, on the one hand, to severe physical and mental aberrations characterized by excruciating headache, projectile vomiting, bradycardia, superficial respiration and semiconsciousness, on the other.

3. The possible mechanism of the increase in intracranial pressure following anoxemia is briefly discussed and the necessity of further study of the particular rôle of brain swelling, besides spinal fluid mechanics and blood circulation pointed out.

4. The oxygen saturation of the arterial blood of different persons exposed to low oxygen is different under the same circumstances. Furthermore, the reduction of the oxygen saturation of arterial blood seems to have no quantitative relationship to the severity of the clinical manifestations; other factors influencing the oxygen tension in the brain itself, such as rate of blood flow and metabolic rate, may play a rôle.

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THE CONTROL OF GASTRIC ACIDITY IN PEPTIC ULCER BY ALKALINIZED POWDERED SKIMMED MILK TABLETS.*

By Paul H. Wosika, M.S., M.D.,

ELIZABETH J. WARD FELLOW IN MEDICINE, INSTRUCTOR IN MEDICINE, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, CHICAGO, ILLINOIS.

(From the Department of Medicine, Northwestern University Medical School and Passavant Memorial Hospital.)

Ideally, the control of the gastric acidity by alkalies should be highly individualized for each patient with peptic ulcer. However, it is appreciated that the frequent assay of the stomach contents to insure this control is not always possible. For this reason it seems desirable to know what methods are most efficient in reducing the corrosive action of the gastric juice.

In previous communications[1,2a,b] an attempt has been made to show that a simplification of a standardized Sippy regimen is possible. An effort has been made to show that there need be no reduction of efficiency in the neutralization of the gastric acidity even when the number of feedings are reduced by one-half. This is

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true when powdered whole milk is substituted for milk and cream. A slightly greater efficiency has been noted when the usual amount of sodium bicarbonate is decreased, which was not found to be true when the sodium bicarbonate was omitted altogether. Of the many combinations of alkalies pressed into tablets of powdered whole milk that were tested, a mixture of 12.5 gm. of powdered whole milk, 0.6 gm. of sodium bicarbonate and 2 gm. of calcium carbonate has been found to be a good, though not a perfect, neutralizing agent.

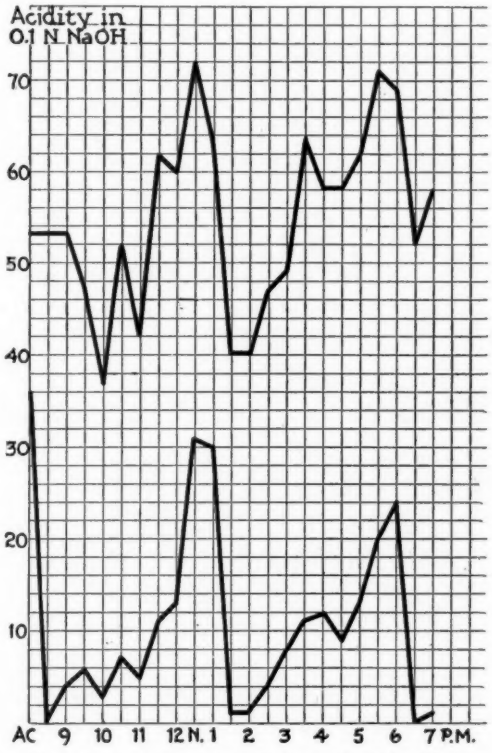

FIG. 1.—Routine Sippy regimen. Average free and total acid curves on 13 patients receiving 90 cc. of milk and cream on the hour and 20 gm. sod. bicarb. and 0.6 gm. calc. carb. on the half hour.

In this present paper it is proposed to show that a larger percentage of patients show an adequate control of hydrochloric acid when powdered skimmed milk tablets are used instead of powdered whole milk, when the amount of alkali is not varied.

Material and Data. Thirteen of the same patients were used for this study who were employed and reported previously.[1] All were male patients with peptic ulcer from the Medical Clinic of North-

western University Medical School. Meals were served at Passavant Memorial Hospital and consisted of the usual foods permitted on fourth week Sippy management. Milk and cream and powders or tablets were given as interval feedings. Aspirations were performed at half-hourly periods.

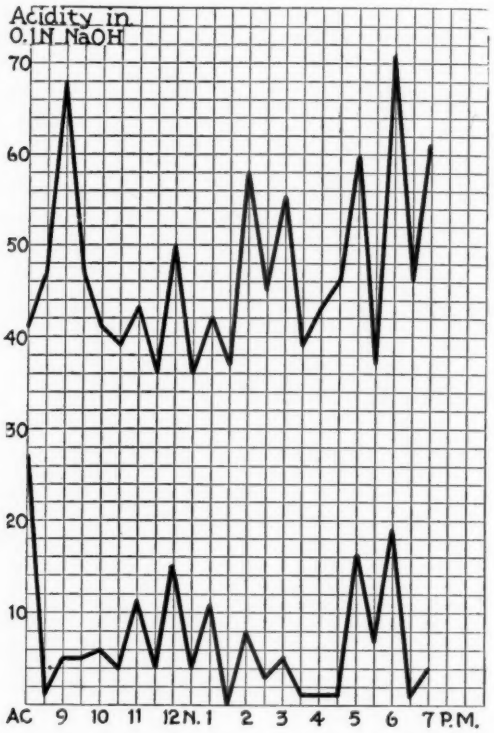

FIG. 2.—Sippy powders with powdered whole milk. Average free and total acid curves on 13 patients receiving 12.5 gm. powdered whole milk (28% butterfat), 2 gm. sod. bicarb. and 0.6 gm. calc. carb. on the hour in 4 tablets with 90 cc. water. The half-hour feeding was omitted.

As a standard for comparison, the results obtained with a routine Sippy management may be seen on Figure 1. These are the average acid curves obtained on the 13 patients in the present series. The titrated total acid values are seen to vary roughly between 40 and 70 clinical units. The free acid curve following the total is seen to descend sharply 3 times daily immediately following the meals allowed. In spite of the milk and cream (90 cc.) each hour allowed on the hour and the routine Sippy powder (2 gm. sodium bicarbonate and 0.6 gm. calcium carbonate) allowed on the half-hour, the acid values increase steadily until at noon the average free acidity

almost equals the fasting values aspirated at 8 A.M. Again, before the evening meal, a peak of 24 clinical units of free acidity is reached.

In Figure 2 the effect of the same amount of alkali with powdered whole milk is considered on the same patients. The difference between Figure 2 and Figure 1 is: 1, That powdered whole milk (12.5 gm.) was substituted for the milk and cream feedings on the

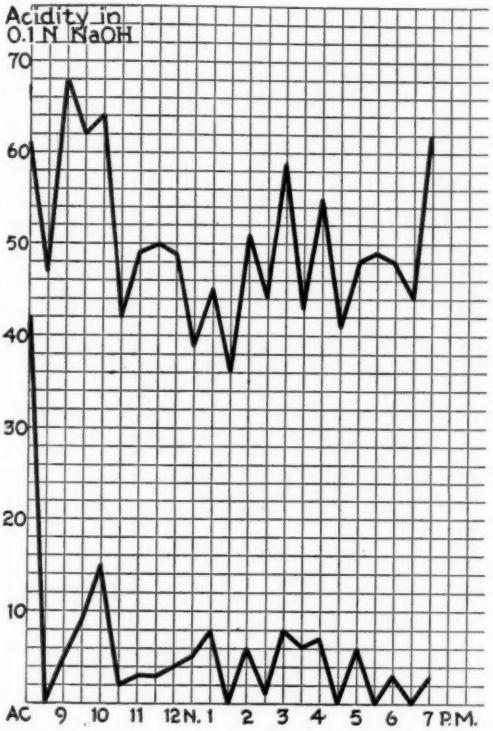

FIG. 3.—Alkalinized powdered whole milk tablets. Average free and total acid curves on 13 patients receiving 12.5 gm. powdered whole milk (28% butterfat), 0.6 gm. sod. bicarb. and 2 gm. calc. carb. on the hour in 4 tablets with 90 cc. water. The half-hour feeding was omitted.

hour; 2, that the same amount of alkali (2 gm. sodium bicarbonate and 0.6 gm. calcium carbonate) was mixed with the powdered whole milk and administered in the form of tablets; and 3, that the half-hour feedings were omitted, although the aspirations were not. Ninety cc. of water was taken with the tablets. Figure 2 shows that while the extremes of the total acid curve is seen to vary between 40 and 70 clinical units, on the whole the values are slightly lower. The neutralization of the free acid, likewise, was not perfect,

as the curve shows. However, high peaks were not reached before meals in the same manner that was noted with the routine Sippy procedure.

Figure 3 shows the average of the free and the total acid determinations on the same patients when the half-hour feedings were omitted. The feedings given every hour consisted of 4 tablets that were made of whole powdered milk (12.5 gm.), but the amount of alkali was changed so that each hourly dose contained 2 gm. calcium carbonate and 0.6 gm. sodium bicarbonate. The total acid curve is seen to be lower than when milk and cream is used with a larger amount of sodium bicarbonate, as well as lower than when pow-

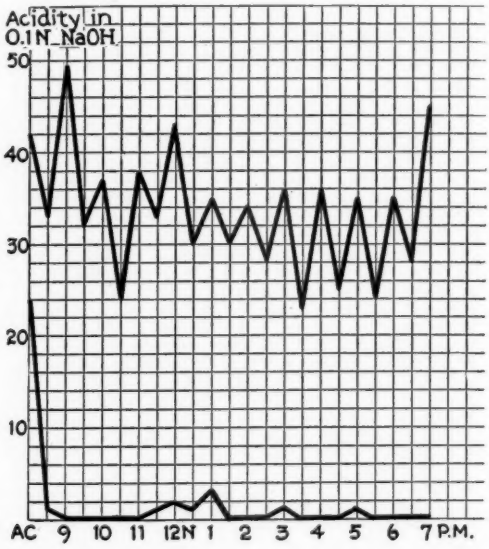

FIG. 4.—Alkalinized powdered skimmed milk tablets. Average free and total curves on 13 patients receiving 12.5 gm. powdered skimmed milk (5% butterfat), 0.6 gm. sod. bicarb. and 2 gm. calc. carb. with 90 cc. water. The half-hour feeding was omitted.

dered whole milk is used with a larger amount of sodium bicarbonate. Except for one period at 10 A.M. the average free acid values were no greater than 8 clinical units. This result is not surprising when one considers previously reported figures.[1]

A more complete picture of acid neutralization is seen in Figure 4. The same patients were administered 4 tablets containing the same amount of alkali that was used in the experiments of Figure 3 (2 gm. calcium carbonate and 0.6 gm. sodium bicarbonate). Instead of the powdered whole milk, however, powdered skimmed milk was substituted in their manufacture. The stimulation afforded the

gastric secretion, as evidenced by the total acid curve, was far less than when the other preparations were used. At the same time the average free acid curve as plotted for the entire day approaches almost perfect neutralization.

Discussion. It is well appreciated that the number of ambulatory patients with peptic ulcer studied for this report represents a small series. The same patients were used, however, in the 4 experiments. Variations in the amount of acid in stomach contents is well known, but is is assumed here that the 13 patients would not show the same physiologic variations (higher or lower) for the same test. Therefore, the alteration of materials administered must be a major factor in the modification of the present results.

That a routine standardized Sippy regimen leaves much to be desired is plainly shown. The noon acid values are almost at the same peak noted for the fasting specimens. This, in spite of the numerous frequent feedings, as has been pointed out, makes numerous aspirations necessary if complete neutralization is to be the goal. Unfortunately, the present studies could not be continued throughout the night.

The results do show that the frequency of the feedings may be reduced with no sacrifice in the efficiency of the neutralization when substitutions are made in the usual Sippy treatment. Powdered whole milk in the form of alkalinized tablets may thus be substituted for whole milk and cream and alkaline powders. An increase in neutralizing efficacy is also noted with a reduction in the amount of soda bicarbonate. Conjectures on these points are considered elsewhere.

Since effectiveness, as well as cheapness (as regards cost to the patient) is to be considered, it seemed reasonable to try the effect of skimmed milk substituted for the powdered whole milk in the tablets. A skimmed milk with 5% butter fat was used, whereas there was 28% in the whole powdered milk. This reduced the calories from approximately 118 in the milk and cream (90 cc.), 62.5 in the powdered whole milk (12.5 gm.), to 48 in the powdered skimmed milk (12.5 gm.). However, this reduction was not considered a serious objection, for an increase in the calories could be achieved with the meals and especially when the more complete neutralization was noted. The exact reasons for the lower acid values when the powdered skimmed milk tablets were used is not apparent at present.

Summary. In a standardized Sippy regimen 12.5 gm. of powdered skimmed milk was substituted for 90 cc. of milk and cream. The amount of sodium bicarbonate was reduced from 2 to 0.6 gm. and the amount of calcium carbonate increased from 0.6 to 2 gm. This was tested on 13 peptic ulcer patients and compared with the results of several other diets previously studied on these same patients.

This material, given once an hour in the form of tablets in addition to the three meals, resulted in a more complete neutralization of the gastric acidity than could be obtained with the routine Sippy procedure and the modifications tried.

Miss Helen Gurley gave expert technical assistance.

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SUBCUTANEOUS EMPHYSEMA COMPLICATING BRONCHIAL ASTHMA.

REPORT OF A CASE AND AN ANALYSIS OF SEVENTEEN PREVIOUSLY REPORTED CASES.

BY LESTER ROSENBERG, M.D.,
ASSOCIATE ATTENDING PEDIATRICIAN, THE BROOKLYN HOSPITAL,
AND
JACOB ROSENBERG, M.D.,
CLINICAL ASSISTANT, OTOLARYNGOLOGY, THE BROOKLYN HOSPITAL, BROOKLYN, N. Y.

(From the Departments of Pediatrics and Oto-rhinolaryngology of the Brooklyn Hospital.)

SUBCUTANEOUS emphysema widespread in character following an attack of bronchial asthma presents so alarming a picture that despite its rarity, its course and prognosis should be more widely known than at present. Considering the frequency of severe attacks of bronchial asthma, it seems strange that this complication is so rare. We have been able to collect only 17 previous cases from the literature.

Case Report. M. T., female, aged 3 years, was admitted to this hospital, September 11, 1935, with the complaint of extreme dyspnea, swelling of the face, neck, trunk and arms following an attack of bronchial asthma. The previous night she had had an attack of bronchial asthma in no way different than the ones she had had innumerable times before. Toward morning the child seemed critically ill. Her dyspnea became worse and the mother noted progressive swelling of the face and chest.

Three weeks before admission she had her tonsils and adenoids removed, and 2 weeks later developed an upper respiratory infection. She had eczema in infancy and bronchial asthma before the age of one year. Her mother suffered from a severe form of bronchial asthma for many years. The patient's general health had been good except for frequent colds. There was a history of food sensitivity in infancy for which desensitization was said to have been attempted.

Physical examination showed a well-developed girl of 3 years, acutely ill, markedly dyspneic with breathing approaching the Kussmaul type. There were bubbling sounds audible from the mucus in the throat. The breath had a fruity odor suggestive of ketosis. Her face was flushed and swollen, being puffier on the right side than the left. The right eye was

TABLE 1.—CASES OF SUBCUTANEOUS EMPHYSEMA COMPLICATIVE BRONCHIAL ASTHMA.

Author.	Age (yrs.)	Sex.	Duration of asthma.	Location of emphysema.	Duration of emphysema (days).
1. Knott,[11] 1850	5	F	Not given	Above sternum spreading lat. and inf. to post. inf. triangle of neck and sup. half of sternum	21
2. Watson,[19] 1885	18	F	Since childhood	Right side of neck and right ant. chest to upper margin of breast	9
3. Calverly,[4] 1899	17	M	11 yrs.	Neck just above clavicles; ant. and post. triangles of neck reaching to level of jaw lat. and ant. as high as thyroid cartilage.	4
4. Whitby,[20] 1905	25	M	Since boyhood	Front and sides of neck; face as far as lower part of forehead, both arms as far as wrist, front of thorax and back as far as upper border of sacrum	The emphysema disappeared gradually.
5. Kahn,[8] 1927	8	F	6 yrs.	Upper part of chest and back, both shoulders, neck, both sides of lower face	10
6. MacDermott[13] 1929	22	M	6 yrs.	Neck, to angle of jaw and just below clavicles	5–6
7. Scheltema,[16] 1931	30	M	First attack	Half the body; face closing, eyes completely and spreading down arms.	7
8. Artagaveytia and Zanzi[1] 1932	18	M	Since infancy	Right side of chest, the neck, over clavicles, eyelids, both upper limbs, except 4 fingers of left hand; inguinal region	8
9. Scremini and Berro,[17] 1932	Not given	F (young)	Not given	Chest and neck	"Few"
10. Mourigan and Cervino,[14] 1932	21	F	Since childhood	Neck, right side of chest, right arm	2
11. Kruysveldt,[12] 1933	22	F	Attacks of shortness of breath since childhood	Entire body from eyes to knees, also scalp, forehead	14
12. Davidson,[5] 1934	9	F	8 yrs.	Upper part of chest post., both shoulders, both arms as far as dorsum of hand, angles of jaw, clavicles and both sides of lower lower face; "crackling in ears"	7
13. Pastorino,[15] 1935	7	F	Not given	Neck, right side, upper ant. portion of thorax, a small portion of upper limbs	6–7
14. Pastorino,[15] 1935	14	M	Since childhood	Neck, face, arms, upper extremities to dorsum of hands; abdomen; upper thighs	10
15. Sheldon and Robinson,[18] 1936	16	M	1 yr.	Left ant. thorax from mid. to post. axillary line, left upper quadrant of abdomen, axilla and ant. and post. triangle of left side of neck	4
16. Kirsner,[10] 1937	38	M	First attack	Face, supraclavicular region, both arms to dorsum of hand	20
17. Bridges,[3] 1937	6	M	3 yrs	Face, ant. and post. triangles of neck, pectoral regions	6
18. Rosenberg and Rosenberg 1938	3	F	Prior to 1 yr. of age	Neck, face, upper extremities, chest, upper abdomen	12

partially closed (Fig. 1). Both eyelids were puffy; the pupils were wide and reacted well to light. The cornea and conjunctivæ were clear. There was extensive subcutaneous emphysema involving the forehead, face, neck, thorax, upper part of abdomen and the arms down to the wrists. Crepitus was easily demonstrated. On the anterior abdominal wall, the emphysema was present only to about the level of the umbilicus.

Auscultation of the chest revealed coarse râles, sonorous and sibilant squeaks audible through the overlying crepitant râles produced by the presence of air in the subcutaneous tissues. The throat was diffusely red and had a glazed appearance; the pharynx was covered with a tenacious stringy mucus. There were dried crusts in the nose. The heart sounds were distant and the rate was rapid and regular.

Roentgen ray on admission (Figs. 2 to 4) showed a marked amount of air in the soft parts about the neck, chest and abdomen. There was spotty density throughout both lung fields, with an area of considerable density in the right upper lobe. The trachea was displaced somewhat to the right. The diaphragm was not elevated. In the lateral view of the chest, the anterior border of the heart was well separated from the anterior chest wall. The area of density in the right upper lobe was considered to be due to atelectasis. About 1 week after admission, September 17, 1935, Roentgen ray (Fig. 5) showed less air in the soft parts about the neck, chest and abdomen. The chest as a whole was clearer than on the previous examination.

Urine examination showed no sugar or albumin but there was a 3+ acetone present. The white blood count was 12,960 with polys, 77%; lymphocytes, 14%; eosinophils, 8%; basophils, 1%. The red blood count was 5,500,000 with 95% hemoglobin. The intradermal tuberculin test was negative with 0.01 mg. and 0.1 mg. The temperatures was never above 100° F.

She was given forced fluids of high carbohydrate content and the usual therapy for bronchial asthma, adrenalin chloride 1:1000 by hypodermic. No attempt was made to treat her subcutaneous emphysema. The alarming nature of her condition persisted for about 12 hours after admission. She improved from her asthmatic attack in the course of a day or so but the subcutaneous emphysema remained for over a week. She was discharged from the hospital, September 18, 1935.

During the past 2 years since the onset of this complication, the child has had 6 or more severe attacks of bronchial asthma with no recurrence of the subcutaneous emphysema.

Comment. In most of the cases reported in the literature, the presence of widespread subcutaneous emphysema complicating an attack of bronchial asthma, produced an alarming picture. In some cases (Kruyseveldt and our case), the dyspnea was so severe and the general condition so alarming that exodus seemed a possibility. Yet uneventful recovery ensued in these and all the other cases recorded.

The pathogenesis of subcutaneous emphysema has been adequately discussed by Artagaveytia and Zanzi,[1] Gallinek,[6] and Berkley and Coffen.[2] Animal experimentation conducted by Kelman,[9] and Joannides and Tsoulos[7] confirms the generally accepted view that the air escapes from one or more ruptured lung vesicles and spreads by way of the root of the lung to the superior

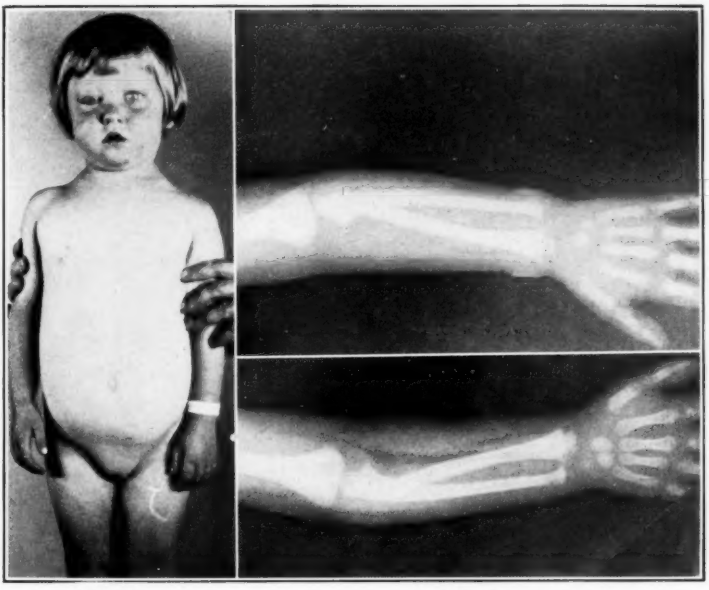

FIG. 1. FIG. 2.

FIG. 1.—September 12, 1935. Partial closure of the right eye, swelling of the face, neck, thorax and abdomen.

FIG. 2.—September 11, 1935. *A*, Imprisoned air in the left forearm. *B*, Imprisoned air in the right forearm.

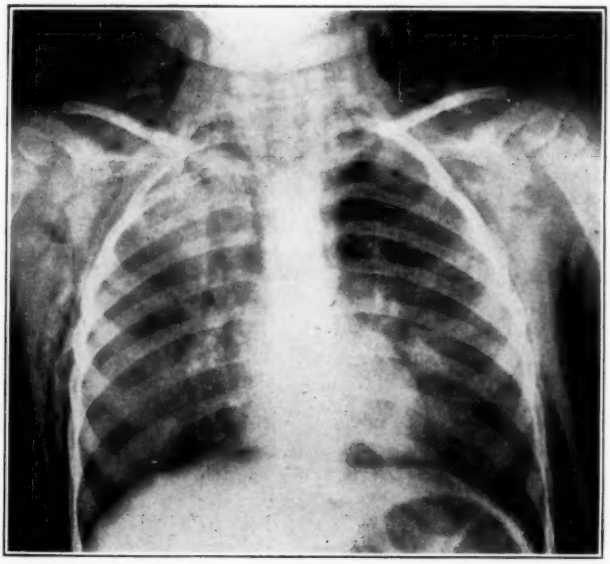

FIG. 3.—September 11, 1935. Anteroposterior view showing marked subcutaneous emphysema of the neck, thoracic wall and upper abdominal wall.

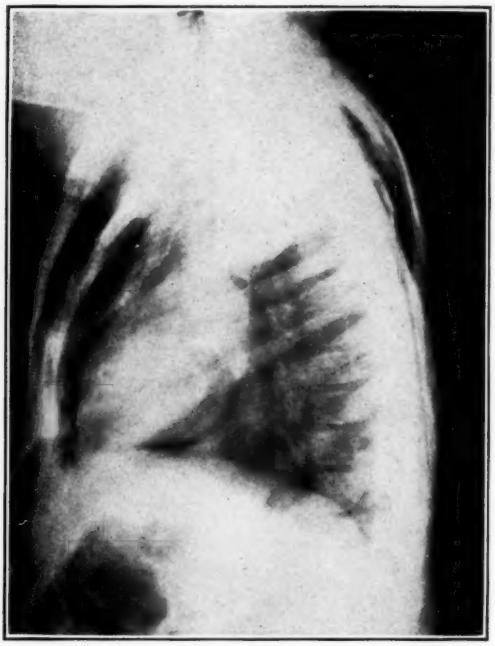

FIG. 4.—September 11, 1935. Lateral view showing subcutaneous emphysema of the anterior chest wall and back.

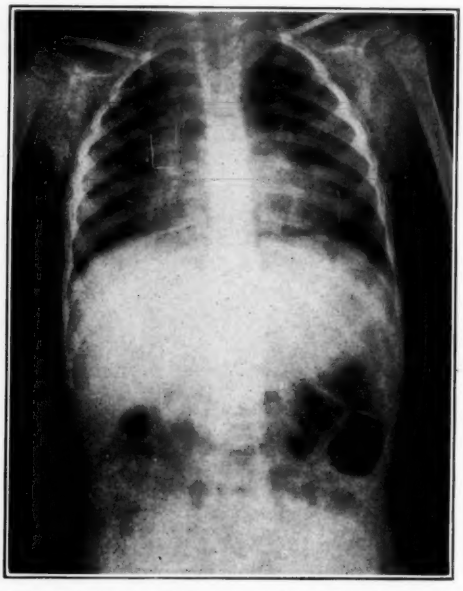

FIG. 5.—September 17, 1935. Anteropostero view showing gradual absorption of the imprisoned air.

mediastinum and neck and thence along fascial planes to the trunk and upper extremities.

Clinically, the subcutaneous emphysema began in the neck in practically all the cases, spread to the face, the upper extremities, the thorax, abdomen and rarely to the thighs (Pastorino,[15] Kruysveldt[12]). In only 2 cases (Scheltema,[16] Kirsner[10]) did the emphysema occur in the first asthmatic attack. All the others regardless of age had had several, often innumerable previous attacks of asthma without complication. The youngest case was our own, a girl aged 3 years, and the oldest, 38 years (Kirsner[10]). Practically all the patients were young individuals: 6 in the first decade of life, 5 in the second, 4 in the third and 2 in the fourth. In 1 case no age was given but the patient was described as a "young female." There was equal division of the sex incidence, half the individuals being male and half female. There have been no recurrences of subcutaneous emphysema despite frequent subsequent attacks of the bronchial asthma.

The shortest duration of the emphysema was 2 days (Mourigan and Cervino[14]) and the longest 3 weeks (Knott[11]), with an average duration of from 7 to 10 days. Knott's case is worthy of special comment. It was not reported by him in the year 1850 as complicating bronchial asthma but his description of a cough with "sonorous and sibilant rhonchi" seems sufficient to include his case in this series.

No other treatment than that of the bronchial asthma itself was employed in any of the cases with the single exception of Kirsner's patient in whom a needle was inserted for release of the imprisoned air.

Conclusions. 1. A case of widespread subcutaneous emphysema complicating an attack of bronchial asthma is described. The alarming picture this condition presents is stressed and the invariably good prognosis discussed.

2. A series of 17 similar cases collected from the literature is analyzed.

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BOOK REVIEWS AND NOTICES.

A PRACTICAL TREATISE ON DISEASES OF THE SKIN for the Use of Students and Practitioners. By OLIVER S. ORMSBY, M.D., Clinical Professor and Chairman of the Department of Dermatology, Rush Medical College of the University of Chicago; Dermatologist to the Presbyterian and St. Anthony's Hospitals, and the Home for Destitute Crippled Children, etc. With revision of the Histopathology and Mycology by CLARK WYLIE FINNERUD, B.S., M.D., Assistant Clinical Professor of Dermatology, Rush Medical College of the University of Chicago, etc. Pp. 1334; 658 illustrations, 3 colored plates. Fifth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, $12.00.

ALL American dermatologists will be glad to see this encyclopedic work by a distinguished author reach its fifth edition. The enormous range of dermatologic phenomena finds here as complete an enumeration as could possibly be expected of even a large one-volume text. The descriptions of disease entities and complexes exhibit the characteristic meticulousness and clarity of the author's writings, and from the more intricate differential material and the therapeutic discussions even the expert can obtain invaluable pointers and slants on one of the largest experiences available in the English language. The photography is excellent, but the illustrations, as in most dermatologic presentations, lean toward extreme and picturesque examples rather than the absolutely characteristic or most frequent lesions.

To those familiar with textbook writing and the problems of succeeding editions, the statement of the publisher that this work, in its present form . . . . "reflects with accuracy the advanced position of present-day dermatology," must be taken with a grain of salt. That the work is intended for the use of practitioners; that it had its foundations laid in more or less unalterable form in the days of morphologic dermatology; that it endeavors to cover a field requiring two separate presentations (dermatology and syphilology), and what amounts to a system rather than a single volume work for either field, these are facts that cannot be evaded. The complete rewriting required for utilization of modern dermatologic advances would be impossible in any revision of an established text with which the Reviewer is familiar. The publishers are therefore to be criticized for allowing exaggerated statements to appear in their advertising. Even a very ordinary review must point out that the physiology of the skin is inadequately presented. The hydrogen-ion concentration of the sweat and the difference between the behavior of apocrine and eccrine sweat glands, for example, is not even mentioned, important though it is for cutaneous etiology. The presentation of allergy, in its relation to cutaneous disease, falls far short of even modest requirements for practical interpretations.

The rewritten section on the cutaneous mycoses, in which this work at first led its field, leaves much to be desired, especially in the field of the intertriginous eruptions. The presentation of syphilis, while modernized on the score of treatment, is not and could not possibly be what the publishers describe as "particularly adequate."

It is, however, an injustice to expect a revision to be a rewriting. For those who, as undergraduate students and as practitioners, desire a dermatologic encyclopedia on conservative lines, with excellent and inclusive differentiation, and an adequate therapy of a more or less empirical type, this work is excellent. J. S.

THE COLLAPSE THERAPY OF PULMONARY TUBERCULOSIS. By JOHN ALEXANDER, B.S., M.A., M.D., F.A.C.S., Professor of Surgery, University of Michigan; Surgeon-in-Charge, Division of Thoracic Surgery, Department of Surgery, University of Michigan Hospital. With Contributions of Chapters III and IV on Physiological Principles and Pathology of Pulmonary Collapse by MAX PINNER, M.D., F.A.C.P., Herman M. Biggs Memorial Hospital, Ithaca, N. Y., etc.; Chapters XI and XII on Pneumothorax by JOHN BLAIR BARNWELL, B.A., M.D., Associate Professor of Internal Medicine, University of Michigan, etc.; Chapter XV on Oleothorax by KIRBY SMITH HOWLETT, JR., M.S., M.D., Resident, Laurel Hills State Tuberculosis Sanatorium, Shelton, Conn. Pp. 705; 367 illustrations. Springfield, Ill.: Charles C Thomas, 1937. Price $15.00.

THE value of collapse therapy in the treatment of pulmonary tuberculosis is discussed in an authoritative and convincing manner. There is need for an equally rational and lucid presentation of the medical treatment of pulmonary tuberculosis with an equally critical analysis of principles, indications, methods and results. If such a work is not forthcoming it will certainly appear that only those unfortunate patients whom the surgeon rejects should rely on medical treatment for the control of their disease. The author estimates that between 50 and 85% of patients with pulmonary tuberculosis should receive collapse therapy in some form.

The author has made a splendid choice of collaborators. The chapters on the physiologic principles and pathology of pulmonary collapse are an able and all too brief consideration of a poorly explored subject. A sound discussion of the use of oleothorax is presented and the section on pneumothorax is a model of thoroughness, clarity and good judgment. The chapters dealing with the indications for various surgical procedures are particularly valuable to the physician. It should be recognized, however, that in many sections of the country the use of phrenic nerve paralysis is rapidly diminishing while the value of artificial pneumothorax has been enhanced as a result of improvements in the technique of closed intrapleural pneumonolysis. The author's emphysis on phrenic nerve operations and his sparing approval of the Jacobeus operation should not be considered representative of present opinion.

The volume is attractive, easy to read and the illustrations, including reproductions of roentgenograms are excellent. Since collapse therapy should be carefully considered for every patient with pulmonary tuberculosis, this work is equally important to the physician and to the chest surgeon. Only 50 pages are devoted to technical procedures of purely surgical interest. This book is highly recommended to all who are interested in the treatment of pulmonary tuberculosis. H. H.

DOCTORS ON HORSEBACK. Pioneers of American Medicine. By JAMES THOMAS FLEXNER. Pp. 370; illustrated. New York: The Viking Press, 1937. Price, $2.75.

SEVEN great men have been selected by the author as types of famous American doctors of more than a century ago—"On Horseback," not because they traveled unsettled regions, like our present-day nurses on horseback of the Appalachian Mountains, but presumably because they lived in the horse stage of transportation. Actually the gig supported the seats of some of these 7 rather than a horse's back. From the Revolutionary period, Morgan and Rush are chosen, the one as "Seer and Continental Soldier," the other as "Saint or Scourge." In the pioneer days of the midwest, McDowell appears as a jazzed "Backwoods Galahad," and Drake

as "Genius on the Ohio," while Beaumont figures with his living laboratory, St. Martin, under the caption "Two Men and Destiny." "The Death of Pain" affords with Morton and Long the occasion for a spirited rehash of the anesthesia controversy. As a Pennsylvanian, the Reviewer takes legitimate pride in the prominent and creditable part played by his university throughout the narrative.

Like many of its prototypes in the field of fictional biography, this book tells a highly picturesque, lively story that should make it a good seller to medical men unacquainted with the history of their professon and to laymen who enjoy looking behind its scenes. The author, with reportorial skill, has unearthed many little known piquant facts about his subjects and, in the words of the cover advertisement, "in this, his first book, has succeeded in combining the two fields" (*i. e.*, fiction and biography). Criticism of inaccuracies might therefore be regarded as carping, but one cannot but regret the occasional misstatement detected even on casual reading. One wishes, too, that somehow the fictional element had been at least indicated as fiction. Also one cannot but wonder at the hidden conflicts in this promising young author which seem to seek escape in his constant carping at the "upper dog." Disproportionate and therefore misleading emphasis is laid on the seamy side of the medicine of those days. The shortcomings of the successful man are rolled under the tongue with obvious gusto; the "aristocrat" is invariably picked on: Shippen's affairs, though he is not one of the subjects chosen, fill a full quarter of the first two chapters and always to his discredit. Rush, admittedly a complex mixture, too often appears in an unfair and disagreeable light; *inter alia*, he is included as one of the principal supporters of the Conway cabal, though qualified historians have rejected this evaluation.

With the above exceptions, criticism may be wholly favorable. The author has delved to good effect in little known manuscript material and so woven his findings into the framework of narratives written in a clear, straightforward style that vivid, and occasionally moving, pictures hold fast the reader's attention. Rush's and Morgan's greatness still manage to shine through the sordid details of contemporary bickerings; Drake's abiding love for Cincinnati, his adopted city, affords a sympathetic explanation of the tortuous career of that hero of the Mississippi Valley; the contributions of Long and Morton are fairly assayed and the problem rested on what constitutes discovery, while all will agree that "Certainly there is enough credit for two to share it." Who will not be convinced also that the heroes of this book and others like them were "strong men who challenged the impossible and won sometimes against greater odds than any which exist today?" E. K.

TWENTY-FIVE YEARS OF HEALTH PROGRESS. A Study of the Mortality Experience Among the Industrial Policyholders of the Metropolitan Life Insurance Company, 1911 to 1935. By LOUIS I. DUBLIN, PH.D., Third Vice-President and Statistician, and ALFRED J. LOTKA, D.SC., Assistant Statistician. With the collaboration of the staff of the Statistical Bureau. Pp. 611; with numerous tables and graphs. New York: Metropolitan Life Insurance Company, 1937.

THE authors present an interesting summary and discussion of health progress in the United States during the priod 1911 to 1935, as evaluated by study of the vital statistics of policyholders, comprising a homogeneous but widely distributed group of some millions of workers and their families. This group differs from the general population of the U. S. Registration area, with which it is compared in considering trends, in being predominatingly urban (over 94%), more evenly distributed as to sex, and a compara-

tively younger group. The study begins in 1911, when the insurance company started its present Health and Welfare campaign.

One is impressed by the extensive gains in life expectancy following, and certainly at least partly due to, the development of a planned and concerted public health activity. In spite of the World War and the depression, this period shows the addition of almost a decade and a half to the average duration of life. Improvement in death rates may be noted all along the line, except in the "degenerative" diseases developing past middle life. The most striking feature of this health picture, however, has been the rapid decline in tuberculosis mortality with its shift in position from first to seventh place in the list of leading causes of death.

The book considers the causes of death under 9 different disease groups. Detailed statistical tables are given for each group, with consideration by color, sex and age, and comparison of trends among policyholders and general population. Discussion is clear and terse, and attempts are made, usually successfully, to derive logical explanations for trends in each group, graphs being used freely.

Rates in policyholders, as would be expected in the group under consideration, are usually higher than in the general population, but they are tending to reduction at a somewhat more rapid rate and are steadily approaching those of the general population.

The book is a wonderful reservoir of interesting and useful statistical material, well arranged and clearly presented and analyzed, and should prove of great value to students, teachers, and public health workers.

H. S.

MENTAL THERAPY. Studies in Fifty Cases. Vols. I and II. By LOUIS S. LONDON, M.D., formerly Past Assistant Surgeon (R.), United States Public Health Service; Medical Officer, United States Veterans' Bureau; Assistant Physician, Central Islip State Hospital, Central Islip, New York, and Manhattan State Hospital, Ward's Island, New York. Pp. 774; 22 illustrations. New York: Covici Friede, 1937. Price, $12.50 the set.

IN this near-orthodox Freudian work are embodied details which positively restrict its sale. Portions of the subject matter: Part I. Metapsychology: evolution of psychotherapeutics, survey of psychoanalysis, meaning of the dream, psychosexual pathology of the child and psychosexual pathology of the sexual instinct. Part II. Psychogenesis and Psychopathology of the Neuroses: analyses of cases showing hysterical neurosis, cardiac neurosis, gastric neurosis, anxiety neurosis with phobia, compulsive thinking, and a doubter; anxiety neurosis in Œdipus situation, anxiety neurosis and sexual impotence, and compulsion neurosis with castration complex. Part III. Paraphiliac Neuroses: case analyses of homosexual neurosis, transvestism, agrophobia, syphilophobia and satyriasis; psychosexual infantilism; sadism and masochism; studies in fetichism and Lesbian love; latent female homosexuality, and female homosexuality—anxiety neurosis. Part IV. Pathogenesis and Psychotherapy of Borderline Neuroses: cases of obsessional, compulsion and anxiety neuroses, latent male and female homosexuality and schizophrenia. Part V. Psychogenesis and Psychotherapy of Schizophrenia: incipient and advanced cases; mechanism in paranoia and analysis of paranoid condition. Part VI. Psychogenesis and Psychotherapy of the Manic Depressive Psychosis: cases of depressed and mixed types.

These many case histories are recorded under such headings as family history, personal history, relationship to father and mother, early and later sexual history, relationship to homosexuality, onset and symptomatology,

sadism and masochism, and mechanisms in conflict. One case includes 24 dreams with interpretations. The case of a young woman showing sadism and masochism covers nearly 42 pages. Stealing, drinking and narcotic indulgence were but minor matters. Her sexual performances were so varied and frequent, that the degenerate women of history stand revealed as lacking in appeal. Were Freud, Adler, Jung, Steckel, Ferenczi and others in nearer accord, psychoanalysis would speak more convincingly. The index is ample, a glossary shows the ever-enlarging nomenclature, but additional methods should appear in a Mental Therapy. N. Y.

SOCIALIZED MEDICINE IN THE SOVIET UNION. By HENRY E. SIGERIST, M.D., William H. Welch Professor of the History of Medicine, The Johns Hopkins University. Pp. 378; illustrated. New York: W. W. Norton & Co., Inc., 1937. Price, $3.50.

SOCIALIZED medicine can exist in its true form only as an integral part of a completely socialized state, and the author presents the characteristics of medical organization that evolve from the doctrines of socialism, which are the foundations of the present Russian government. After learning the Russian language, the author spent the summers of 1935 and 1936 in Russia, and not only made many observations of the medical organization, but also collected much documentary material regarding the official plans for medical service in the Soviet Union. He has long been interested in the theories of socialism, and presents a picture of Russian medicine as one phase of a rapidly moving and vast human drama, in which socialism is on trial. He has aimed to describe the advantages of socialized medicine, as compared with the medicine of Western Europe and of America, with which he is widely familiar, and has not attempted a critical analysis of its weaknesses or of the obstacles to its practical application.

The author points out that the Soviet Union is the first country to socialize medicine, and the first to consider the protection of the health of all the people a public function of the state. Although he recognizes inadequacies and shortcomings, both as to facilities and administration, his study leads him to conclude that medicine in the Soviet Union today is the beginning of a new period, the period of preventive medicine, as contrasted with the period of curative medicine of the past five thousands years.

Medicine in Russia today is an integral part of a great experiment in human relations, which will be observed and studied with such interest for years to come. The author has presented a significant phase of this fundamental experiment in a book which throws light on the Russia of today, illuminating a broader field than that related strictly to health and to disease G. R.

THE ENDOCRINES IN THEORY AND PRACTICE. Articles Republished from the British Medical Journal. Pp. 278. Philadelphia: P. Blakiston's Son & Co., 1937. Price, $3.50.

THIS is a publication in book form of a series of articles which were written on request of the *British Medical Journal* in 1936 and 1937 by Langdon-Brown, Dodds, Harington, Biggart, McCarrison, Fraser, Robson, and many others. The form of presentation is very simple, and obviously intended for those in general practice who do not have the time for following at first hand the complicated ramifications of the literature on hormones. Occasionally personal viewpoints, not generally accepted, obtrude; but on the whole anyone needing a book of this type will find it more accurate than most simplifications tend to be. I. Z.

SURGERY OF THE SYMPATHETIC NERVOUS SYSTEM. By GEORGE E. GASK, C.M.G., D.S.O., F.R.C.S. (ENG.), Emeritus Professor of Surgery, University of London; Consulting Surgeon, St. Bartholomew's Hospital; and J. PATERSON ROSS, M.S. (LOND.), F.R.C.S. (ENG.), Professor of Surgery, University of London; Surgeon and Director of the Surgical Unit, St. Bartholomew's Hospital. Pp. 191; 49 illustrations (4 in color). Second edition. Baltimore: William Wood & Co., 1937. Price, $4.50.

IN this book, the thoraco-lumbar portion of the autonomic nervous system is considered without the cranial and sacral portions. No morbid anatomy is given since none is known, except when there are tumors of the ganglia. Previously, these authors regarded the late results of sympathectomy as depending upon "the powers of the sympathetic to regenerate, and of the organs to function independently of their nerve supply;" but it is now believed the later results depend mostly upon the nature of the disease. Among new features included are the clinical gradings and prognosis in Raynaud's disease, recognition of localized structural disease of the main arteries, afferent pathways in the sympathetic system, and sympathectomy for dysphagia. The results obtained are not always clearly stated, but they are concerned with disorders of the circulation: operations for sympathetic denervation of the extremities and effects of cervico-thoracic ganglionectomy; disorders of the visceral motor mechanism in the alimentary canal and urinary tract; in dysmenorrhea, vesical and rectal pain, angina pectoris, and in causalgia. It is suggested that individuals who show "temperament" may have imperfect cerebral cortical control of centers in the hypothalamus. There is a selected bibliography at the end of each chapter and a fair index. The appearance of a second edition in less than 4 years speaks of increasing interest in this constructive work. N. Y.

MATERNAL DEATHS—THE WAYS OF PREVENTION. By IAGO GALDSTON, M.D., Secretary, Medical Information Bureau of the New York Academy of Medicine. Pp. 115. New York: The Commonwealth Fund, 1937. Price, paper, 50c.; cloth, 75c.

THIS clear, concise and factually accurate discussion of the several aspects of maternal mortality is intended for laymen, physicians and allied medical services. The author has drawn upon several of the recent reports on the subject, notably the study in New York City by a committee of the Academy of Medicine, for the basic material. The various factors concerned in maternal deaths, antepartum care, attendant, place and manner of delivery, influence of Cesarean section and of anesthesia and analgesia, abortion are assayed in terms of responsible influence. The answer, what can be done? as he so clearly shows concerns the entire community, public and profession, hospital and schools, health departments and community organizations. The part each element should play is honestly and straightforwardly given us. P. W.

SHORT YEARS. The Life and Letters of John Bruce MacCallum, M.D., 1876–1906. By ARCHIBALD MALLOCH. Pp. 343; illustrated. Chicago: Normandie House, 1938. Price, $3.50.

J. B. MACCALLUM'S scientific achievements as a student–well-known to medical students of the Reviewer's day, who were only a few years his junior—have inevitably faded into the back-ground as time has marched on. This sympathetic account by a personal friend not only perpetuates his example of notable achievement early in scientific life; but also gives an

inspiring account of a sensitive soul's brave and successful fight to the end against chronic ill health. MacCallum's later important California studies on purgatives led Jacques Loeb to recognize him as a remarkably skillful investigator of the type "whom we may designate as discoverers. His results were obtained quickly, were made secure beyond doubt, and were put into such shape that they could easily be demonstrated by him." "St. John," as Osler nicknamed him, was to Osler "one of the most brilliant young men whom it has been my lot to teach." A prolific letter-writer and diarist, a story writer and poet of merit, he was undoubtedly one of the greatest of that notable group that Canada has lent to medicine in this country. He is then a conspicuous example of Plautus' truth, "Quem di diligunt, adolescens moritur." This account of his life and letters will be read with interest by many beside his personal friends. E. K.

PHYSIOLOGICAL CHEMISTRY OF THE BILE. By HARRY SOBOTKA, Chemist to the Mount Sinai Hospital, New York. Pp. 202; 4 illustrations. Baltimore: The Williams & Wilkins Company, 1937. Price, $3.00.

THE present volume is a very admirable attempt to collect and correlate physiological, pharmacological and pathological data upon bile. Both experimental and clinical material are collected under the various subjects chosen for discussion. Two short chapters deal with the origin and quantity of hepatic secretion. Approximately 50 pages are devoted to the composition of the bile; one-third of this space being upon the bile acids and their interrelations, while the remainder is devoted to the other normal constituents and the chemical properties inherent in such a complex secretory product. The chemistry and physiology of the bile pigments were excluded, for its inclusion would require extensive reference to blood pigments and pyerol chemistry. Non-physiological constituents of bile, and the processes of detoxification are discussed briefly. The influence of various chemical, physical and biological factors that can be considered either as choleretics or cholagogues are reviewed extensively. Evidence is summarized also upon the presence of bile acids outside of the biliary tract, *e. g.*, in feces, urine, normal and icteric blood, etc. The concluding chapter is upon the effects of bile acids upon chemical and biological reactions and processes, including their effects in digestion and resorption of fat, their action on enzymes, their effects upon blood cells and microörganisms, and the pharmacological effects on the various organs of higher animals. A bibliography of nearly 1200 references is appended.

Analytical methods for determining the various important bile constituents are not discussed in this volume, this being reserved for a companion volume on the "Chemistry of Sterids." I. R.

PEDIATRIC UROLOGY. In two volumes. By MEREDITH F. CAMPBELL, M.S., M.D., F.A.C.S., Professor of Urology, New York University College of Medicine, and Associate Attending Urologist, Bellevue Hospital, etc. With a Section on Bright's Disease in Infancy and Childhood, by JOHN D. LYTTLE, A.B., M.D., Assistant Professor of Diseases of Children, College of Physicians and Surgeons, Columbia University, etc. Pp. 1116; over 1350 illustrations and 2 colored plates. New York: The Macmillan Company, 1937. Price, $15 the set.

THESE two volumes break new ground for a medical text, and one need not look for comparisons by which to weigh it, for such do not exist. "Pediatric urology is still in its diaper age," states the author, and he has made this

effort "to indicate to practitioners in general, and to pediatrists and urologists in particular, the clinical aspects of urologic disease in infants and children." His background has been his work, now well known to his colleagues for many years, with over 1000 pediatric beds in 4 large New York hospitals, and also 4 Out-patient Departments. To this is added the tabulated studies of 12,080 postmortem examinations on infants and children. From this experience of over 10 years the statement is made that, "about half of all children suffer some form of urologic disturbance before they reach puberty. Although a large portion of these conditions are of a minor nature, and many pass unrecognized, the field of Pediatric Urology still remains of unexpected enormity."

Volume I starts with methods of examination and diagnosis, and it is rapidly developed that no method of investigation now used in the adult is denied the infant or child. There follow chapters on the many-sided problem of obstructive uropathies; the wide field of anatomy and the anomalies; and then the long-mooted topic of urinary infections. This last chapter is a monograph that stands alone, and would that every pediatrician and every urologist could read it. (Surely the world would be better!)

Volume II starts with a chapter on Bright's disease by the author's collaborator, Dr. Lyttle: followed by chapters devoted to genital disease; urogenital injuries; calculus disease; tumors; neuromuscular disease; enuresis; and urosurgery.

The text is beautifully and excellently illustrated, and where necessary, both tabulations and case reports are inserted. The bibliography is complete, as likewise the index. One could expatiate in glowing terms on this welcome addition to urology, and silently pray that the pediatric world will mark, heed and inwardly digest. A. R.

DIE WERKE DES HIPPOKRATES. Part 16. Der Samen / Das Werden des Kindes / Das Herz / Die Geistesstörung / Die Tollwut / Die Nieswurzanwendung. (On Generation; On the Nature of the Infant; On the Heart; On Mental Disturbance; On Hydrophobia; On the Administration of Hellebore.) Pp. 95, Price, Rm. 7.50. Part 17. Die Leiden / Die Krankheiten, 1. Buch. (Of Affections; Of Diseases, Book 1.) Pp. 102. Price, Rm. 8. Part 16. Ubersetzt von DR. MED. RICHARD KAPFERER, Facharzt für Physikalisch-diätetische Behandlung. Part 17. Herausgegeben von DR. MED. RICHARD KAPFERER, Bad Wörtshofen und München, unter Mitwirtung von Prof. DR. GEORG STIDER, Würzburg, u. a. (To be published in 25 parts costing ca. Rm. 100, card binding.)

PART 16. "Generation" and "The Nature of the Child" are the largest of the treatises in this booklet. They probably, according to Kapferer, were originally combined as the fourth book of "Diseases." The work is chiefly concerned with the normal and abnormal processes that develop the seed into the embryo and the infant. Hippocrates' comparison of the effect of natural forces on fauna and flora support his important opening generalization that the laws of Nature are omnipotent. The impotence of eunuchs is of course recognized, and the explanation of various congenital anomalies is attempted. One can read into the text beliefs on causality and heredity that are surprisingly compatible with modern views.

The 10 short pages on "The Heart" include remarkable descriptions of that organ, its chambers, valves and appendages. Though the author appreciated the central importance of the heart and recognized the vessels coming to and leading from the two ventricles, a true circulation is far from being visualized. The left ventricle, the seat of the soul, is regarded as the place where the nourishing air coming from the lungs is cooked with blood ele-

ments to make the arterial blood. That the left ventricle was not nourished by visible blood was proven to the author by the fact that it was found empty in slaughtered animals.

The sections on Mental Disturbance, Hydrophobia and Administration of Hellebore, are taken by Kapferer from the newly discovered version of the "Letters of Hippocrates" in the Urbinas 68 s XIV Manuscript. They are regarded by the editor as truly Hippocratic both because of their lines of thought and diction and because they fill in a section that, though lacking in the accepted Corpus Hippocraticum, is referred to in the work on "The Sacred Disease." There mental disease is divided into two groups caused by retention and mucus in the brain and by influx of bile into the brain, respectively. Only the former is treated, while the latter forms the topic of the 19th letter, but in this manuscript in ten-fold longer form. The Administration of Hellebore is from the 21st letter. These important additions to the Corpus appears here in a modern language for the first time.

PART 17. "The Affections," usually regarded as of Cnidian origin, was said by Galen to have been written by Polybos, the son-in-law of Hippocrates. Apparently intended for the medical apprentice (not the laity), it sketches the general causes of disease before taking up treatment. Derangements of bile and mucus are most important, whether from macrocosmic (heat, cold, etc.) or microcosmic (diet, effort, wounds, sexual activity, impressions on special senses) causes. The seven fluxes from the head (to the ear, nose, eyes, thorax, abdomen, skin and joints and the vertebral column) produce various diseases in each region, to be treated by various means, physical, dietary, surgical and medical. Enemas, emetics and purgatives are favorites used in many different conditions.

"The Disease" also is said by Galen and Diocorides to come from Polybos, but by others to be Cnidian. It also treats of the macrocosmic and microcosmic causes of disease. Discussion of the course of wound healing and of diseases leads to outlines of correct diagnosis. The pathogenesis of empyema, "erysipelas" and ulcers (tuberculosis) of the lung, of fever, chills, sweats, is explained on the basis of the doctrine of the four humors. E. K.

AN ANALYSIS OF THE DE GENERATIONE ANIMALIUM OF WILLIAM HARVEY. By ARTHUR WILLIAM MEYER, Professor of Anatomy, Stanford University. Pp. 167; illustrated. Stanford University: Stanford University Press, 1936. Price, $3.00.

THOUGH Harvey will undoubtedly always be chiefly remembered for his immortal discovery of the circulation of the blood, admirers have not been lacking to extol his later work on the Development of Animals. It is indeed surprising, then, that the author of this Analysis should have found that, in the 144 Harvaeian Orations which have been given in London, this book should never have received adequate attention and indeed never even been mentioned until 1872. He has only been able to find three recent works that have given more than scant attention to *De Generatione*, so that the present volume is the first considerable analysis of a work that was much longer and more complex than its more famous predecessor. In the present work one passes from a consideration of the times and of previous and contemporary embryologists to an analysis of the treatise itself, Harvey's version of epigenesis, his aphorism *ex ovo omnia* (so frequently distorted into *omne vivum ex ovo*), his views on fertilization and so on. One is forced to agree with the author that the same method that led Harvey to the successful solution of the problem of the circulation failed to discover the mysteries of generation or even materially to promote the search. *De Motu* "was a brief, clear, convincing, and decisive demonstration, revolutionary

in both nature and effect while the *De Generatione* was long, obscure, speculative, and inconclusive in both nature and effect." This is not permitted to hide the merits of Harvey's work: his use of the scientific method whenever possible, his numerous keen observations and shrewd reasoning, his many-sided and long-sustained attempt to prove *ex ovo omnia*, and the superiority of his book to those on the subject by his contemporaries. It is also true and worth emphasizing that Harvey's eminence is so well established by his immortal discovery that it need not be supported by exaggerated claims for his less successful effort. E. K.

A Dissertation on Acute Pericarditis. By Oliver W. Holmes. Introduction by James F. Ballard, Director, Boston Medical Library. Pp. 39. Boston: The Welch Bibliophilic Society, 1937. Price, $7.50.

Though Holmes did not study in the Harvard Medical School, he was given his M.D. degree by Harvard in 1836, after having taken courses in a private medical school, "walked the hospitals" of Paris for two years and practised a year in Boston. For his dissertation, which was then a prerequisite for the degree, he wrote on Acute Pericarditis; but as Ballard explains in the Introduction, the manuscript has remained unnoticed in the Boston Medical Library, not having been mentioned by either his biographer, Morse, or his bibliographer, Ives. It now appears in print for the first time. Though, like most dissertations, it contributed little more than the current knowledge of the subject, this in itself is of interest on account of the great productive activity of the French School at that time. More interesting is the characteristic vein of humor that frequently crops up to the surface and the fact that, for reasons not given, the thesis was prepared "entirely in the span of little more than 3 days." E. K.

A Text-book of Ophthalmic Operations. By Harold Grimsdale, M.B., F.R.C.S., Consulting Ophthalmic Surgeon to St. George's Hospital; Consulting Surgeon to the Royal Westminister Ophthalmic Hospital, and Elmore Brewerton, F.R.C.S., Consulting Ophthalmic Surgeon to the Metropolitan Hospital; Consulting Surgeon to the Royal Westminister Ophthalmic Hospital. Pp. 322; 105 illustrations. Third edition. Baltimore: William Wood & Co., 1937. Price, $6.00.

The third edition of this text contains the newer operations for detachment of the retina. The illustrations as in the first edition are not good. The book can only be recommended as a résumé of the methods employed by English ophthalmic surgeons. F. A.

Chemistry of the Brain. By Irvine H. Page, A.B. (Chem.), M.D., Hospital of The Rockefeller Institute for Medical Research, New York. Pp. 444. Springfield, Ill.: Charles C Thomas, 1937. Price, $7.50.

The growth of our knowledge of sterols and their very wide biological importance has resulted, as is to be expected, in the publication of a number of excellent monographs upon the subject. The present volume by Dr. Irvine H. Page is not merely a further treatment of sterol chemistry. If Dr. Page were writing in the language of J. L. W. Thudichum, a history of whose pioneer efforts in brain chemistry prefaces the work, the book might bear the following descriptive title: "The chemistry, chemical pathology and physiology of the brain and nerve tissue, giving the clinical

applications of the same, as well as the interrelationships of the organ of thought to the body as a whole."

Such a title the Reviewer believes would cover more aptly the generous extent of Dr. Page's work. Not only is the chemistry of the sterolic brain substances treated, but adequate space is devoted to what is known of carbohydrate metabolism, water balance, nitrogen metabolism, vitamin and enzyme activity, and oxidation-reduction processes as they apply to brain and nerve tissues.

The treatment is most readable throughout, and, in a number of instances provocative. For example, in the last chapter, "The Brain and Thought," Dr. Page discusses, among other things, the ambiguity in the word "ought," used by scientists on the one hand or by religionists on the other. It is not clear to the Reviewer whether Dr. Page has settled the question "ought a man murder his wife?" They are, of course, countless problems which are raised in work of this sort, and which future research no doubt will solve.

The "Chemistry of the Brain" is recommended highly to all workers in the biological sciences, and should prove of especial interest to those engaged in research and treatment of nervous and mental disease.

D. D.

DIE DIFFUSIONSANALYSE AM BLUTPLASMAGEL. Ein Neuer Weg der Blutforschung. By RUDOLF BUCHER. Pp. 123; 70 illustrations (30 in color). Basel: Benno Schwabe & Co., 1937. Price, Fr. 30.

LIESEGANG rings of silver bichromate were produced in citrate plasma which, after addition of potassium bichromate, had been transformed into a gel by the addition of Ca and then covered by silver nitrate solution. The procedure described in detail allows a fairly satisfactory reproducibility of the ring formation in regard to time of appearance as well as distances between the rings. Comparing a great number of plasma samples, characteristic differences in the arising structures were observed depending upon the origin of the plasma and upon physiological conditions. Age, sex, species are shown to be of importance. Arterial plasma is different from venous plasma. After strong bleeding the plasma gives no rings at all. Anesthesia with ether or chloroform, shock experimentally produced, *e. g.*, by mechanical stimulation of the abdominal sympathetic, slow down the appearance of the ring structure. The results are illustrated by excellent pictures, 30 of them in colors.

R. H.

PRACTICAL PHYSIOLOGICAL CHEMISTRY. By PHILIP B. HAWK, M.S., PH.D., President of the Food Research Laboratories, Inc., New York City, and OLAF BERGEIM, M.S., PH.D., Associate Professor of Physiological Chemistry, University of Illinois College of Medicine, Chicago. In Collaboration with BERNARD L. OSER, PH.D., Director of the Food Research Laboratories, Inc., New York City, and ARTHUR G. COLE, PH.D., Assistant Professor of Physiological Chemistry, University of Illinois College of Medicine, Chicago. Pp. 968; 281 illustrations. Eleventh edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, $8.00.

THE eleventh edition of this well known textbook contains much new material. Many chapters have been entirely rewritten, the list marking the fields of biochemistry in which most notable advances have been made—the vitamins, enzymes, endocrines, digestion, bile, putrefaction and detoxication, blood and tissue analysis and the teeth. As ever it is unexcelled as a practical manual.

E. W.

MAN AGAINST HIMSELF. By KARL A. MENNIGER. Pp. 485. New York: Harcourt, Brace and Company, 1938. Price, $3.75.

UNDER appropriate captions, detailed study is made of such varied subjects as asceticism and martyrdom, neurotic invalidism, alcoholic addiction, anti-social behavior, psychoses, self-mutilations, malingering, impotency and frigidity. Inspired by Freud's hypothesis of man's propensity for self-destruction, the author endeavors to show that by a sort of psychosynthesis, these variant, instinctively destructive forms of suicide, may lead one logically to a process of self-preservation.

Asceticism and martyrdom are accorded most space. Among historic martyrs is Simeon Stylites who was idolized by his parents, but whose brutal repulsion contributed to their death. A quote from Lecky's description of the saint's monastery life reads: "A horrible stench, intolerable to the bystanders, exhaled from his body, and worms dropped from him whenever he moved and they filled his bed . . ." After having built three pillars, he mounted the last, which was 60 feet high, and there lived for 30 years. During an entire year, "St. Simeon stood upon one leg, the other being covered with hideous ulcers, while his biographer was compelled to stand by his side, to pick up the worms that fell from his body, and to replace them in the sores, the saint saying to the worm, 'Eat what God has given you.'" A less gloomy church version of the saint is available.

As in "The Human Mind," the author employs a non-technical, popular, dramatic style, which has given us a book that is interesting and stimulating to the imagination. However, an implication by Havelock Ellis is recalled: " . . . the psychoanalyst is a kind of spider who spins his pathological web-complex so vividly and so elaborately . . . in the hope that somewhere . . . the fly must be entangled." N. Y.

CLINICAL ALLERGY. Due to Foods, Inhalants, Contactants, Fungi, Bacteria and Other Causes. Manifestations, Diagnosis and Treatment. By ALBERT H. ROWE, M.S., M.D., Lecturer in Medicine in the University of California Medical School, San Francisco; Chief of the Clinic for Allergic Diseases of the Alameda County Health Center, Oakland, Calif., etc. Pp. 812. Philadelphia: Lea & Febiger, 1937. Price, $8.50.

SIX years ago, Dr. Rowe published his excellent book on food allergy. The present volume is obviously the result of expanding that volume to cover the whole field of allergy. The author has certainly succeeded in covering the field, but the major emphasis, one may say overemphasis, remains on food allergy. Thus after chapters on the nature, mechanism, origin and characteristics of allergy and the diagnosis of allergy, come chapters on the "Treatment of Food Allergy by Elimination Diets and General Measures," and on "Gastrointestinal Allergy," before asthma or other respiratory tract manifestations of allergy are considered. However, one may well pardon the overenthusiasm for food allergy on the part of a man who has made so many important contributions to our knowledge of the subject. Of particular value is the enormous amount of clinical case material which the author has gathered, both from his own large experience and the literature, to illustrate the many phases of clinical allergy. There are numerous and well selected references to the huge literature in this field, but theoretical matters are at times vaguely stated or not interpreted with strict accuracy. There are, on the whole, surprisingly few mistakes even for a first edition (*e. g.*, pyrethrum *leaves* instead of *flowers* used as insecticides; attributing to Baum priority in the exclusively allergic etiology of nasal mucous polyps). No one interested in the field of allergy can afford to be without this important work and all internists will find it a very helpful book of reference.

R. K.

TREATMENT BY DIET. By CLIFFORD J. BARBORKA, B.S., M.S., M.D., D.Sc., F.A.C.P., Department of Medicine, Northwestern University Medical School, Chicago. Pp. 642; 8 illustrations. Third edition, revised. Philadelphia: J. B. Lippincott Company, 1937. Price, $5.00.

THAT a third edition has been called for since its appearance in 1934 testifies to the popularity of this very practical presentation of the subject. Discussions of the clinical aspects of current knowledge of the vitamins, the use of protamin-zinc insulin and an enlarged section on diet in the treatment of obesity are the new material in the volume. R. K.

NEW BOOKS.

The Biology of Pneumococcus. The Bacteriological, Biochemical, and Immunological Characters and Activities of Diplococcus Pneumoniæ. By BENJAMIN WHITE, PH.D., with the collaboration of ELLIOTT STIRLING ROBINSON, M.D., PH.D., and LAVERNE ALMON BARNES, PH.D. Pp. 799; illustrated. New York: The Commonwealth Fund, 1938. Price, $4.50.

Eighth International Congress of Military Medicine and Pharmacy and Meetings of the Permanent Committee, Brussels, Belgium, June 27–July 3, 1935. Report of CAPTAIN WILLIAM SEAMAN BAINBRIDGE, M.C.-F., U.S.N.R., Ret., Member of the Permanent Committee for the Delegation of the United States of America. Pp. 114; illustrated.

The Time Has Come. . . . (The Harveian Oration Delivered Before the Royal College of Physicians of London on St. Luke's Day, 1937.) By SIR ARTHUR HURST, M.A., D.M. (OXON.), Senior Physician to Guy's Hospital; Fellow of the College. Pp. 42. London: Headley Brothers, n.d. Price, 5/–.

The two hundred and eighteenth Harvey Oration, though it perforce neglects some of the instructions of the immortal donor, complies at least with the exhortation to search and study out the secrets of Nature by way of experiment. The orator has sketched the recent advances in knowledge of disordered gastric physiology in relation to anemia—Beaumont, Spallanzani, Fenwick, Faber, Castle, Hurst and Bell—and to the pathogenesis of gastric carcinoma.

The Treatment of Clinical and Laboratory Data. An Introduction to Statistical Ideas and Methods for Medical and Dental Workers. By DONALD MAINLAND, M.B., CH.B., D.Sc. (EDIN.), Professor of Anatomy, Dalhousie University, Halifax, Nova Scotia. Pp. 340; 23 illustrations. London: Oliver and Boyd, 1938. Price, 15/–.

The Patient and the Weather. Vol. IV, Part 3, Organic Disease. Surgical Problems. By WILLIAM F. PETERSEN, M.D. With the assistance of MARGARET E. MILLIKEN, S.M. Pp. 651 (lithoprinted); 482 illustrations. Ann Arbor: Edwards Brothers, Inc., 1938. Price, $10.00.

Claude Bernard, Physiologist. By J. M. D. OLMSTED, Professor of Physiology, University of California. Pp. 272; illustrated. New York: Harper & Brothers Publishers, 1938. Price, $4.00.

Handbook on Social Hygiene. Edited by W. BAYARD LONG, M.D., Attending Dermatologist and Director of Dermatology and Syphilis Clinics in St. Luke's Hospital, New York, etc., and JACOB A. GOLDBERG, M.A., PH.D., F.A.P.H.A., Secretary, Social Hygiene Committee, New York Tuberculosis and Health Association, and Social Hygiene Council of Greater New York. With a Foreword by EDWARD L. KEYES, M.D., Professor Emeritus of Clinical Surgery (Urology) in Cornell University Medical College, New York. Pp. 442; 62 illustrations. Philadelphia: Lea & Febiger, 1938. Price, $4.00.

Contributions to Medical Research. Anniversary Volume. Scientific Contributions in Honor of JOSEPH HERSEY PRATT on his Sixty-fifth Birthday. (Reprinted from articles appearing in Annals of Internal Medicine.) Pp. 983; illustrated. Printed by Lancaster Press, Inc., Lancaster, Pa., 1937. Price, $7.00.

Das Rheumabuch des Doctor Ballonius. Nach der Rheumaschrift des Lateinischen Textes. Gulielmi Ballonii, Liber de Rheumatismo et Pleuritide Dorsali, Paris, 1642. Deutsch Herausgegeben von DR. WALTER RUHMANN, Specialarzt für Innere Krankheiten in Berlin. Pp. 66; 1 illustration. Mittenwald: Arthur Nemayer, 1938. Price, Rm. 3.

Zeitschrift fur Rheumaforschung. Band 1, Heft 1, Januar, 1938. Herausgegeben von DR. P. KÖHLER, GEH. SAN-RAT, Leiter d. Staatl. Rheumaheilanstalt u. d. Sanatoriums Bad Elster, PROF. DR. RUD. JÜRGENS, Stellv. Dir. d. Univ.-Klinik für natürl. Heil- und Lebensweisen, Berlin. Für den Referatenteil: DR. H. KAETHER, Univ.-Klinik für natürl. Heil- und Lebensweisen, Berlin. Unter Mitwirkung von Th. FAHR, Hamburg; F. FRIK, Berlin; G. HOHMANN, Frankfurt a. M.; P. ROSTOCK, Berlin; R. SCHOEN, Leipzig; A. SLAUCK, Aachen; H. VOGT, Breslau. Pp. 40; 13 illustrations. Dresden: Theodor Steinkopff, 1938. Price, Quarterly, Rm. 7.50; Yearly, Rm. 30.

Journal of Neurophysiology. (Issued Bi-monthly). *Vol. 1, No. 1, January, 1938.* Editorial Board: J. G. DUSSER DE BARENNE (Yale), J. F. FULTON (Yale), R. W. GERARD (Chicago). Advisory Board: E. R. ADRIAN (Cambridge); P. BAILEY (Chicago); P. BARD (Baltimore); G. H. BISHOP (St. Louis); F. BREMER (Brussels); D. BRONK (Philadelphia); E. VON BRÜCKE (Innsbruck); S. COBB (Boston); H. DAVIS (Boston); U. ERBECKE (Boon); J. C. ECCLES (Sydney); J. ERLANGER (St. Louis); W. O. FENN (Rochester); A. FORBES (Boston); H. S. GASSER (New York); R. GRANT (Helsingfors); W. R. HESS (Zurich); MARION HINES (Baltimore); DAVENPORT HOOKER (Pittsburgh); R. LORENTE DE NÓ (New York); W. PENFIELD (Montreal); H. PIÉRON (Paris); S. W. RANSON (Chicago); G. VAN RIJNBERK (Amsterdam); C. S. SHERRINGTON (Ipswich). Pp. 85; illustrated. Springfield, Ill.: Charles C Thomas, 1938. Price, $6.00 per volume.

The Thousand Forms of Disease. By R. P. BYERS, M.A. Pp. 29. Boston: Super-university Publications, 1938. Price, $1.50.

A Biological Approach to the Problem of Abnormal Behavior. By MILTON HARRINGTON, M.D., Psychiatrist, Institution for Male Defective Delinquents, Napanoch, N. Y.; Formerly Consultant in Mental Hygiene, Dartmouth College. Pp. 459; illustrated. Lancaster: The Science Press Printing Company for the Author, 1938.

Introduction to Ophthalmology. By PETER C. KRONFELD, M.D., Professor of Ophthalmology, The Peiping Union Medical College. Pp. 331; 32 text illustrations and 5 plates. Springfield, Ill.: Charles C Thomas, 1938. Price, $3.50.

Clinical Roentgen Therapy. Edited by ERNST A. POHLE, M.D., PH.D., F.A.C.R., Professor of Radiology; Chairman, Department of Radiology and Physical Therapy, University of Wisconsin, Madison, Wisconsin. Foreword by GEORGE W. HOLMES, M.D., Roentgenologist to the Massachusetts General Hospital and Clinical Professor of Roentgenology in Harvard Medical School, Boston. Pp. 819; 199 illustrations and 1 colored plate. Philadelphia: Lea & Febiger, 1938. Price, $10.00.

Workbook in Elementary Diagnosis for Teaching Clinical History Recording and Physical Diagnosis. By LOGAN CLENDENING, Professor of Clinical Medicine, University of Kansas. Pp. 167; illustrated. St. Louis: The C. V. Mosby Company, 1938. Price, $1.50.

Practical Procedures. (The Practitioner Handbooks.) Edited by SIR HUMPHRY ROLLESTON, BT., G.C.V.O., K.C.B., M.D., F.R.C.P., and ALAN A. MONCRIEFF, M.D., F.R.C.P. With a Preface by SIR DAVID WILKIE, O.B.E., M.D., M.CH., F.R.C.S., F.A.C.S., F.R.S.E. Pp. 293; 66 illustrations. London: Eyre and Spottiswoode (Publishers) Ltd., 1938. Price, 10s. 6d.

On Thought in Medicine (*Das Denken in der Medizin*). By HERMANN VON HELMHOLTZ. An Address delivered August 2, 1877, on the Anniversary of the Foundation of the Institute for the Education of Army Surgeons. Introduction by ARNO B. LUCKHARDT. (Reprinted from Bulletin of the Institute of the History of Medicine, Vol. 6, No. 2, February, 1938.) Pp. 27; 2 illustrations. Baltimore: The Johns Hopkins Press, 1938. Price, 75c.

Diabetes Insipidus and the Neuro-hormonal Control of Water Balance: A Contribution to the Structure and Function of the Hypothalamico-hypophyseal System. By CHARLES FISHER, PH.D., W. R. INGRAM, PH.D., and S. W. RANSON, PH.D., M.D., Institute of Neurology, Northwestern University Medical School. Pp. 212 (lithoprinted); 71 illustrations and 26 tables. Ann Arbor: Edwards Brothers, Inc., 1938. Price, $5.00.

The Brain and Its Environment. By JOSEPH BARCROFT, Professor of Physiology, Cambridge University. Pp. 117; 30 illustrations. New Haven: Yale University Press, 1938. Price, $2.00.

On a New Gland in Man and Several Mammals (*Glandulæ Parathyreoideæ*). By IVAR SANDSTRÖM [Upsala Läkareförenings Förhandlingar, 1879–80, **15**, 441–471.] Translated by CARL M. SEIPEL, Dr. Med. Dent. Edited by CHARLOTTE H. PETERS and J. F. FULTON. With biographical notes by Professor J. AUGUST HAMMAR. Pp. 44; 1 illustration and 3 plates. Baltimore: The Johns Hopkins Press, 1938. Price, $1.00.

NEW EDITIONS.

X-rays and Radium in the Treatment of Diseases of the Skin. By GEORGE M. MACKEE, M.D., Professor of Clinical Dermatology and Director of Department of Dermatology (Skin and Cancer Unit), New York Post-Graduate Medical School and Hospital, Columbia University; Consulting Dermatologist, St. Luke's Hospital, etc. Pp. 830; 308 illustrations, 31 charts and 2 colored plates. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $10.00.

Recent Advances in Pathology. By GEOFFREY HADFIELD, M.D., F.R.C.P. (LOND.), Professor of Pathology in the University of London; Pathologist to St. Bartholomew's Hospital, etc., and LAWRENCE P. GARROD, M.A., M.D., B.CH. (CAMB.), F.R.C.P. (LOND.), Professor of Bacteriology in the University of London; Bacteriologist to St. Bartholomew's Hospital, etc. Pp. 420; 65 illustrations. Third Edition. Philadelphia: P. Blakiston's Son & Co. Inc., 1938. Price, $5.00.

Pneumonia and Serum Therapy. By FREDERICK T. LORD, M.D., Clinical Professor of Medicine, Emeritus, Harvard Medical School, etc., and RODERICK HEFFRON, M.D., Field Director, Pneumonia Study and Service, Massachusetts Department of Public Health, 1931–1935. Pp. 148; 10 figures and 10 tables. Revised edition of Lobar Pneumonia and Serum Therapy. New York: The Commonwealth Fund, 1938. Price, $1.00.

Medical Dictionary. II. Part. German-English. By JOSEPH R. WALLER, M.D., and MORITZ KAATZ, M.D. Pp. 238. Seventh Edition. Wien: Franz Deuticke, 1938. Price, M. 7.

This pocket sized dictionary should be useful to many English speaking readers of German medical works. It can hardly be expected to be as satisfactory as larger volumes.

Management of the Sick Infant and Child. By LANGLEY PORTER, B.S., M.D., M.R.C.S. (ENG.), L.R.C.P. (LOND.), Dean, University of California Medical School, and Professor of Medicine, etc., and WILLIAM E. CARTER, M.D., Director, University of California Hospital Out Patient Department, etc. Pp. 874; 94 illustrations. Fifth Revised Edition. St. Louis: The C. V. Mosby Company, 1938. Price, $10.00.

PROGRESS
OF
MEDICAL SCIENCE
THERAPEUTICS

UNDER THE CHARGE OF
CARY EGGLESTON, M.D.,
ASSISTANT PROFESSOR OF CLINICAL MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK CITY,
AND
SOMA WEISS, M.D.,
ASSOCIATE PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

THE USE OF SULPHANILAMIDE IN THE TREATMENT OF VARIOUS INFECTIONS.

WITHIN the past 2 years there has come into prominence a large number of reports concerning the experimental and clinical use of sulphanilamide and related chemical compounds in the treatment of various infections. While these chemicals have been used in a wide variety of infections, those resulting from hemolytic streptococci, meningococci, gonococci, and urinary tract infections have received most attention. It is the purpose of this short review to summarize a few of the more important results that have been obtained in these infections, and to emphasize the more important toxic manifestations of these compounds in man.

Terminology. Inasmuch as a number of compounds have been used in the treatment of various infections, it is well to summarize the nomenclature. The results recorded in the literature following the use of these various drugs have varied somewhat so that it is important to designate the proper name to the drug that is employed in each instance. Table 1 summarizes a few of the various drugs that have been used most widely. Of these, sulphanilamide and prontosil soluble have had the widest use in this country.

TABLE 1.—NOMENCLATURE.

1. Sulphanilamide—also known as
   - Para amino benzene sulphonamide
   - Prontosil album
   - Prontylin
   - Stramid
   - Streptocide
2. Prontosil—also known as
   - Prontosil red
   - Prontosil flavum
   - Sulphamido-chrysoidine
3. Prontosil Soluble

Pharmacology of Sulphanilamide. From the studies of Marshall, Emerson, and Cutting[14] it is known that the drug is absorbed from the gastro-intestinal tract with remarkable rapidity. Maximum concentrations in the blood are reached within 4 hours after its ingestion. It diffuses through all of the tissues, and resembles urea in its approximately even distribution throughout the body. Marshall and his associates have been able to show that skeletal muscles, heart muscle, liver, lung, and spleen contain the same concentration as blood. Skin contains slightly less, brain contains about two-thirds the concentration of blood, and bone and fat contain the drug in much lower concentration than blood. The drug is excreted in the urine and nearly 100% of the amount ingested can be recovered. Part of the drug becomes acetylated during its passage through the body but most of it is free and readily detected. Marshall has found that sulphanilamide is excreted entirely by glomerular filtration and that 70 to 80% of it is reabsorbed by the tubules. When there is impaired renal function sulphanilamide is excreted more slowly. For this reason it is necessary to give the drug to patients with renal insufficiency in smaller amounts and for a shorter duration of time. Since it is absorbed from the gastro-intestinal tract almost as rapidly as from the subcutaneous tissues, it is not necessary to give the drug subcutaneously in any patient unless he has excessive vomiting. The drug diffuses into the cerebrospinal fluid in about 80% of the concentration in the blood. It is not necessary, therefore, to give this drug intrathecally in cases of meningitis.

Treatment of Hemolytic Streptococcal Infection. *Puerperal Fever.* Extensive studies on the effect of sulphanilamide, prontosil soluble, and prontosil have been carried out in cases of puerperal fever by Colebrook and Kenny[5] and Colebrook and Purdie.[6] Keefer[11] has reported results in a small group of cases. Impressive results have been obtained with prontosil soluble, prontosil, and sulphanilamide. In Colebrook and Purdie's recent paper the comment is made that their results with sulphanilamide seem to be less effective than those obtained with prontosil soluble and prontosil. However, the average stay in hospital was reduced from 31.3 days before the use of the drug to 19.7 days following its use. Moreover, they have been able to reduce their average fatality rate from 22.8% in cases before the use of prontosil soluble and sulphanilamide to 5.5% in cases following its use. In a footnote, Colebrook and Purdie state that the death rate in all of their cases of infection by hemolytic streptococci treated with these drugs since August, 1936, has been 7%.

It is now recognized that the average fatality rate for all cases of puerperal sepsis due to hemolytic streptococci is between 15 and 25%. It is lowest in those cases with only a localized infection of the endometrium, and highest in those with bacteremia, peritonitis, or thrombophlebitis of the pelvic veins with metastases (50 to 70%). It might be anticipated, then, that the most striking results from the use of sulphanilamide would be obtained in those cases in which the death rate is lowest, and this turns out to be the case. In the bacteremic cases reported by Colebrook and associates, the fatality rate was 71% in the untreated cases over a 4-year period, and during the period in which patients were treated with prontosil soluble or sulphanilamide

the fatality rate was 40%. In their last paper there were 15 bacteremic cases with 8 deaths. In some there was a mixed infection. In the cases limited to the uterus, vagina, and perineum there were no deaths.

From the studies so far reported it would appear, then, that in puerperal fever due to hemolytic streptococci the use of sulphanilamide, prontosil, and prontosil soluble reduces the fatality rate, especially in infections limited to the uterus, vagina, and perineum, and even in cases of bacteremia and peritonitis. The duration of the infection seems to be shortened, the hospital stay reduced, and the spread of the infection prevented.

Erysipelas. The fatality rate in erysipelas is highest under the age of 6 months and after the age of 50 years, especially in patients with bacteremia and debilitating diseases. From the reports of a few cases it would appear that both prontosil soluble and sulphanilamide are distinctly helpful in the treatment of this disease. There are cases in which recovery occurred in newly-born infants with bacteremia, and the fatality rate seems to be reduced in infants under 6 months of age. Furthermore, there is evidence that the lesion stops spreading and that the duration of fever is shortened in some cases following the exhibition of the drug. While it is difficult to decide just what effect these drugs have in individual cases, since the natural history of erysipelas varies so widely from case to case, evidence in accumulating that is highly suggestive of its beneficial effects.

Hemolytic Streptococcal Bacteremia. When hemolytic streptococcal infection is accompanied by bacteremia, the prognosis is extremely grave. In general, the fatality rate is in the neighborhood of 70%, although it varies with the site of the focus, the age of the patient, and the treatment employed. I have been able to collect 50 cases of bacteremia from the literature, including 12 cases of my own, in which bacteremia was observed in a patient treated with either prontosil soluble or sulphanilamide. The fatality rate in these cases was 32%, a figure that is distinctly lower than any untreated group. These observations are to my mind among the most convincing that these drugs are of distinct value in hemolytic streptococcal infection.

Hemolytic Streptococcal Meningitis. Everyone is agreed that hemolytic streptococcal meningitis is the most serious of all hemolytic streptococcal infections. It has been established that the fatality rate in these cases is in the neighborhood of 98%. From 1901 to 1937 there were 110 recorded recoveries in the literature (Gray,[8] Trachsler[18]). Since 1937 with the introduction of prontosil soluble there are at least 40 cases reported that have recovered, and while it is too soon to say what the fatality rate will be in this disease, it is safe to assume that more than one-half of the cases can be treated with a satisfactory outcome. These results are indeed very outstanding and remarkable.

Tonsillitis and Scarlet Fever. So far there is little convincing evidence that the clinical course of scarlet fever or tonsillitis is affected by the use of sulphanilamide or prontosil soluble. Whether or not it will reduce the number of suppurative complications in this group of infections will have to be decided from additional studies.

In brief, then, there seems to be no doubt that sulphanilamide and related compounds have a profound effect on the course of hemolytic

streptococcal infections. The most striking effects have been observed in puerperal sepsis, hemolytic streptococcal meningitis, and in cases of bacteremia. There are other infections in which it is difficult to decide, or in which the present data are insufficient to draw an accurate conclusion. These include tonsillitis, sore throat, and erysipelas.

Treatment of Meningococcal Infection. Following the observations of Proom,[16] Brown,[3] Branham and Rosenthal,[2] and others that sulphanilamide and related compounds are capable of protecting mice against fatal infection when the mucin technique of Miller is used, these drugs have been employed in the treatment of meningococcal meningitis. As related above, sulphanilamide diffuses into the cerebrospinal fluid with ease when it is taken by mouth, and it is present in about 80% of the concentration of the blood, so that it is not necessary to give it intraspinally. Schwentker[17] reported a 15% fatality rate in 52 patients treated for meningococcal meningitis. Place[15] of the South Department of the Boston City Hospital informs me that their fatality rate has been 25% in the cases treated with sulphanilamide alone. This is approximately one-half the fatality rate obtained in both clinics from which the reports came when antiserum was used. I have treated 2 patients with excellent results. While it would be premature to say that sulphanilamide was as effective in the treatment of meningococcal infection as specific antiserum, the evidence available at present indicates that it is an effective form of treatment and it has the advantage that one does not have to introduce foreign protein to the cerebrospinal system.

Treatment of Gonococcal Infection. Following the report of Colston and Dees[7] a great many patients have been treated with sulphanilamide for gonococcal infection, including urethritis, cervicitis, gonococcal ophthalmia, vulvovaginitis of children, pelvic peritonitis, and arthritis. The reports that have been written concerning the results are somewhat conflicting. There seems to be no doubt that in some series of cases at least, one-half of the instances of urethritis are completely relieved within 7 days of treatment. In others, the course is more chronic and, in some, it seems to be completely ineffective. It has been emphasized on a number of occasions that following the administration of the drug by mouth, the discharge from the urethra diminishes, the symptoms subside, but gonococci can still be obtained from urethral and prostatic exudates. These observations serve to emphasize the importance of careful examination of exudates for the presence of gonococci, even after the acute stage of the process has subsided.

It has been found, from a study of the blood of patients receiving sulphanilamide, that the bactericidal power for the gonococcus increases greatly, and that this property of the blood is maintained as long as the drug is continued in adequate dosage. Moreover, it has been possible in a few cases to sterilize infected synovial fluid within 2 days after the exhibition of the drug. From such studies it seems likely that sulphanilamide will be effective in preventing bacteremia, and that it will be an aid in clearing foci of infection. In spite of the reports in which failures have been recorded, there are good experimental and clinical reasons for believing that the use of this drug in the treatment of gonococcal infection will prove to be a most helpful therapeutic agent.

Treatment of Urinary Tract Infections. One of the characteristic features of sulphanilamide is its bacteriostatic effect on the growth of various bacteria. This property has been used in the treatment of urinary tract infections due to *B. coli*, *Hemophilus influenzæ*, *B. proteus*, and *Staphy. aureus*. Helmholz[10] also states that sulphanilamide is bactericidal and that it can be used in the acute stage of urinary tract infection. He maintains that it is active in an alkaline urine and can be used in the face of renal insufficiency. In his experience it has had favorable action in all of the infections except *Strep. fæcalis*. Bliss and Long[1] have reported failures with the use of sulphanilamide in streptococcal infections due to Group D (Lancefield). Our experience with the drug indicates that the drug is bacteriostatic and frequently reduces the number of organisms without producing a complete sterilization of the urine. In some cases, however, the organisms disappear entirely during the administration of the drug and reappear once it is discontinued. In others, complete recovery follows and, in another group, no effect seems to be evident. That it is a drug of value in these infections, no one can deny, but it is entirely too early to say just what its field of greatest usefulness will be in the future.

Toxic Manifestations of Sulphanilamide. While sulphanilamide has a relatively low toxicity for animals it is known that certain individuals respond in a way that is exceedingly alarming and, indeed, dangerous. The various toxic manifestations are summarized in Table 2.

TABLE 2.—TOXIC MANIFESTATIONS.

Symptoms and signs.	Time of appearance.	Treatment.	Outcome.
Cyanosis	First or second 24 hours	None—unless there are symptoms of anorexia; then discontinue drug	Recovery is prompt.
Nausea Vomiting Giddiness Weakness	First 24 hours or longer	None—it is usually not severe enough to discontinue drug	
Anemia	3 to 7 days	Stop drug immediately Force fluids to 3000 cc. daily Blood transfusions	Recovery from blood transfusion.
Agranulocytosis	14th day or later	Stop drug Pentnucleotide Blood transfusion	Fatal in most cases.
Fever	7th to 9th day Usually continues 2 to 6 days Varies from 101° to 106°	Discontinue drug Force fluids	Complete recovery.
Skin rash	7th to 9th day Usually accompanied by fever	Discontinue drug Force fluids	Complete recovery.

Cyanosis. Cyanosis of the skin and mucous membranes following the administration of sulphanilamide is exceedingly common and, in fact, when adequate dosage is given it is almost always present. It has been attributed to the presence of sulphhemoglobin and/or methemoglobin in the blood as these pigments have been demonstrated by some investigators. In the vast majority of cases showing cyanosis

it is not possible to demonstrate either methemoglobin or sulphemoglobin in the blood by spectroscopic analysis. Marshall and Walzl[13] have shown that the hemoglobin content of the blood in cyanotic individuals is the same when it is determined by the oxygen capacity method as it is when the total iron content of the blood is determined. There was no evidence in most of the cases that they examined that abnormal pigments were present. It was also clear that the blood cells were not interfered with insofar as normal oxygen exchange was concerned. From these observations it was suggested by Marshall and Walzl that the cyanosis and the dark color of the blood when it is withdrawn from a vein is due to a black oxidation product which stains the red blood cells. In view of the fact that abnormal pigments have been found in the blood of some cyanotic individuals and that they may appear soon after the administration of sulphates, such as magnesium or sodium sulphate, it is well to examine the blood of cyanotic individuals for abnormal pigments so that these do not accumulate in large enough amounts to prove deleterious to the tissues. Inasmuch as practically all of the patients receiving sulphanilamide become cyanotic and since there is no evidence that every individual who becomes cyanotic has sulph- or methemoglobinemia, there are no good reasons for discontinuing the drug on account of the presence of cyanosis alone.

Acidosis. One of the changes that take place in the blood following the use of these drugs is the development of a reduced carbon dioxide combining power and the symptoms of acidosis. To prevent this, sodium bicarbonate is usually given at the same time as the sulphanilamide. The precise mechanism by which acidosis is produced is not absolutely clear, although it is known that large amounts of sodium are lost in the urine in these patients.

Hemolytic Anemia. One of the more serious complications that must be looked for is an acute hemolytic anemia. It was first described by Harvey and Janeway,[9] later by Kohn[12] and others, and we have observed 3 cases. From our own experience and that of others the characteristic features of this complication are: (1) a rapidly progressive anemia coming on within 3 to 5 days following the administration of the drug; (2) polymorphonuclear leukocytosis; (3) jaundice and signs of diminished hepatic function in some cases; (4) prompt recovery following withdrawal of the drug, the use of blood transfusions, and forcing fluids to 3000 cc. a day.

The anemia, which is often severe, may develop with great rapidity so that the erythrocyte count and hemoglobin content of the blood may decline to levels of 30 to 40% of normal within a few days after the drug has been started. This decline in the red cells is accompanied by the appearance of anisocytosis, pallor, many nucleated erythrocytes and reticulocytes. The total leukocyte count is usually increased, varying between 20,000 and 87,000 per c.mm. There are many immature neutrophils and myelocytes; platelets are normal in number.

Jaundice has been a feature of most of the patients showing anemia but it has not been present in all. Two of Harvey and Janeway's cases showed no jaundice clinically, although there was evidence of increased blood destruction as determined by the presence of increased urobilinogen in the stools and urine. Bile pigment appears in the urine of some

cases and there is evidence of impaired hepatic function as determined by the bromsulphthalein excretion tests. In a case reported by Kohn hemoglobinuria was a feature.

In 1 case studied by us the fragility of the red cells in varying concentrations of salt solution was normal. The Donath-Landsteiner and the Ham phenomena were not present. We were unable to detect any evidence of an intravascular hemolysin. Recovery has followed the use of blood transfusions in all cases, but it is a most serious complication.

In brief, then, one of the complications of this drug is a hemolytic anemia that occurs within the first 5 days following treatment. It can usually be controlled by discontinuing the drug, forcing the fluid intake to 3500 cc. a day, and giving whole blood transfusions. Inasmuch as it can develop rapidly and occur without jaundice, the hemoglobin and erythrocyte count should be followed carefully during the first week of treatment.

Optic Neuritis. Bucy[4] described an isolated instance of optic neuritis occurring in a young girl, aged 16, following sulphanilamide. Vision was reduced for a period of 4 days. There was central scotoma for red and blue and relative scotoma for white. This appeared after the use of one tablet of sulphanilamide, although she had received the drug on several previous occasions for 2 days. Recovery was complete following the withdrawal of the drug.

Skin Eruptions and Fever. Within 4 to 14 days, usually 7 to 10, following the administration of sulphanilamide cutaneous eruptions with fever may appear and persist from 2 to 9 days. The temperature may vary from normal to 106° F., the average being 101° to 103° F., and this may persist from 2 to 9 days, usually 2 to 4. While in about one-half the cases the fever is accompanied by an eruption, it may occur alone without any other signs of toxic manifestations of drug reaction.

The skin rashes have varied considerably and have consisted of urticaria, exfoliative dermatitis, morbilliform eruption, edema of the face and arms, hemorrhagic and purpuric rashes, scarlatiniform eruptions, and in a few cases the eruption appeared only after exposure to sunlight. All of the rashes usually cleared up completely following discontinuance of the drug.

Agranulocytosis. This is a most serious complication of sulphanilamide therapy. With a few exceptions most of the reported cases have ended fatally. Several interesting and important features have been brought out from a study of these cases. The first is that no case of agranulocytosis has been reported as occurring before the fourteenth to the sixteenth day after the onset of treatment. It has also been stated that the leukocyte count frequently drops following the discontinuance of the drug. It is not always clear from the reported cases, however, that the decrease in the leukocyte count occurred in an abrupt manner, since leukocyte counts were not done daily. It is also a striking fact that when death occurred it usually did so within 2 to 3 days after the onset of agranulocytosis. Fatal cases serve to emphasize the importance of making repeated leukocyte counts in all individuals who are receiving the drug for a week or more.

Dosage of Drug. There is no absolute agreement concerning the dosage of sulphanilamide. Most workers have elected to give the drug so that it will be present in the circulating blood in amounts of at least 10 mg. per 100 cc. In general, we have usually given, as an initial dose, 0.6 gm. per kilo of body weight and then followed this dose by 0.6 gm. every 4 hours. In most adults of average weight we have given 8 gm. during the first 24 hours. Usually after that time we continued the drug in daily doses of 4 gm. each. The sulphanilamide of the blood is determined every 2 days during its administration. Hemoglobin and leukocyte counts are done daily. If the concentration in the blood increases above 10 mg. %, the dose is reduced.

CHESTER S. KEEFER, M.D.

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RADIOLOGY

UNDER THE CHARGE OF
ALBERT MILLER, M.D.
AND
CHARLES G. SUTHERLAND, M.D.
CONSULTING PHYSICIANS, SECTION ON ROENTGENOLOGY, MAYO CLINIC, ROCHESTER, MINN.

CHRONIC GASTRITIS.

MORGAGNI (1761) was the first to call attention to gastritis. After him, Broussais (1808) did a great deal of original work on this subject, and in his opinion gastritis was responsible for a number of conditions, such as septicemia, typhoid fever and meningitis; ascites, cerebral hemorrhage and pneumonia were considered by him to be complications of gastritis.

It was not long, however, until it was recognized that Broussais' conception was erroneous; what he had considered to be gastritis was found to be postmortem changes. Beaumont enlarged the knowledge

of gastritis by his experimental contributions. The situation underwent a sudden change when Kussmaul invented the gastroscope (1867) and used it in the following year to examine the human stomach. The subject of the experiment was a professional sword swallower. A rigid instrument was used, the lighting was indirect, and no satisfactory view of the stomach was obtained. Mickulicz, about 1881, again attempted gastroscopy with a rigid instrument, but the results were unsatisfactory.

With the invention of the gastric tube, the anatomic conception of gastritis was relinquished in favor of the functional conception. Hypersecretion, hyperacidity, subacidity and anacidity became independent clinical units of what was considered to be nervous dyspepsia (Leube). Achylia gastrica was assumed to be a purely functional disturbance. But the pendulum was found to swing back to the anatomic conception of the disease, and Hayem (1892), by preventing postmortem changes, demonstrated the frequent occurrence of inflammation of the stomach.

Hayem's statements were confirmed by the development of gastric surgery, which furnished a large amount of material for study in the form of resected stomachs. Immediate fixation of resected specimens made it possible to rule out postmortem changes. Later, improved methods of clinical investigation were developed: roentgenology (Rendich, Forssell, Cole, Berg, Gutzeit) and gastroscopy (Schindler, Gutzeit, Korbsch, Henning) contributed greatly to the present knowledge of gastritis.

In a symposium presented before the Radiological Society of North America the comparative value of gastroscopy and Roentgen examination of the stomach was discussed; the theme of the discussion was largely the subject of chronic gastritis. Coincidental with the publication of the papers of this symposium, Ansprenger and Kirklin presented a critical analysis of the roentgenologic aspects of this same subject.

NOTE: A bibliography is appended covering all the references without specific direction as to the individual reference.

Roentgenology is a comparatively new science. It honors the name of the discoverer of the new light which was the foundation of the science. He modestly named it the *x*-ray and this appelation is still more widely used than that of roentgenology and its derivatives. The announcement of the discovery came in an elaborate description of the revolutionary new ray printed in the morning edition of the Wiener Presse. The news was quickly copied by other continental papers and was cabled on the evening of January 6, 1896, from London to most of the civilized countries of the world. The possibilities of the *x*-ray as a diagnostic agent in medicine were discussed before the Berlin Medical Society the day previous to, and before the Society of Internal Medicine in Berlin the day of the announcement of the discovery. By the end of February, 1896, the method was in comparatively general use as a new diagnostic procedure in many countries.

Hemmeter, writing on "Photography of the Human Stomach by the Roentgen Method" on June 18, 1896, quoted Becker as having succeeded in making roentgenograms of the stomach and a loop of small intestine of a guinea pig by distending both with liquor plumbi subacetatis. Hemmeter suggested this same medium be introduced into

the viscus by means of a deglutible gutta-percha bag and withdrawn therefrom by aspiration. At that time he did not suggest bismuth, but used it later by intravisceral insufflation.

Loaded tubing passed into the stomach could do little more than outline its greater curvature, but the position of the viscus was thereby roughly estimated.

The suggestion to use the Roentgen method in the study of gastric motor function was made by Bowditch in 1896. Among the first recorded scientific investigation of the gastro-intestinal tract by means of the Roentgen ray were those of W. B. Cannon. His first work on the movements of the stomach was presented before the American Physiological Society in May, 1897. Cats were employed in his researches by Cannon who wrote that "the mixing of a small quantity of subnitrate of bismuth with the food allows not only the contractions of the gastric wall, but also the movements of the gastric contents to be seen with the Roentgen rays in the uninjured animal during normal digestion. An unsuspected nicety of mechanical action and a surprising sensitiveness to nervous conditions have thereby been disclosed." Cannon's preliminary report (May, 1897) antedated the work of Roux and Balthazard on frogs, dogs and man.

In September, 1899, Williams, assisted by Cannon, fed 2 children subnitrate of bismuth mixed with bread and milk and made observations, with the aid of a fluorescent screen, of the movements of the stomach during respiration and of the changes in shape during digestion. In a third child that he examined, using the fluoroscope, he also made roentgenograms at intervals of 1 to 2 hours. Williams observed the intestinal tract using capsules filled with opaque material and the colon with rectum-injected air.

Boas and Levy-Dorn (1896) conducted screen studies, using contrast capsules, and Benedict (1898) observed by fluoroscopic screen the intra-alimentary behavior of capsules containing reduced iron and attempted to localize them by making roentgenograms.

Lester Leonard (1897), by washing out the stomach and introducing bismuth, was able to show, in a case of gastroptosis "the area of the stomach through the bones of the pelvis."

Rieder (1904) advocated in a published paper the ingestion of large doses of subnitrate of bismuth, which he demonstrated to be entirely harmless, as a substitute for artificial insufflation of the stomach with gas, a method not entirely devoid of danger. By means of this method it was possible to demonstrate roentgenographically, in the most detailed manner, the contour, as well as the size, shape and position of the different parts of the gastro-intestinal canal. Moreover, he stated, the motor functions could similarly be studied; according to the experimental work of Pavlow on dogs, the motor movements were the same for bismuth as for milk and water. Rieder prophesied that the extensive use of the Roentgen procedure in the examination of the digestive tract would be of great value in the field of medical practice and would in the future contribute materially to the support of the diagnosis of gastric and intestinal diseases. This work furnished a stimulus to contemporary investigation and sounded an early note of prediction as to the future importance of this function of radiology.

Hemmeter (1906) published the results of his researches. He produced ulcers in rabbits and cats experimentally by creating a defect in the gastric lining and coated the denuded surface with subnitrate of bismuth and, after closing the abdomen, was able to visualize this region by means of the Roentgen ray. He then succeeded in demonstrating such experimentally produced denudations by introducing a bismuth suspension into the stomach of the animal through a tube and studying them by fluoroscopic observation. By having patients drink such a barium suspension, with the stomach empty, he succeeded in visualizing an ulcer in 3 cases; 1 of his patients was operated on and the roentgenologic findings were confirmed.

Reiche (1909) demonstrated an accessory pocket, created by perforation of a gastric ulcer on to the pancreas. He also established the fact of gastric retention to a pathologic degree as a result of gastric ulcer.

Haudek (1910) elaborated upon and popularized the Roentgen method of diagnosis. He verified its practical value in numerous cases that were proved to be correct by surgical investigation or at autopsy. Haudek, and later Eisler, referred to the significance of the spastic contractions of the musculature observed in many cases with mucosal ulceration. These contractions not infrequently led to the development of a functional hour-glass stomach, which existed for years without producing cicatricial contraction.

Forssell (1912) initiated the study of mucosal relief patterns and showed that the rugal folds of the stomach had an independent mechanism, so that they varied from time to time on account of active movements of the mucous membrane itself throughout the entire alimentary canal, and were due to contractions of the muscularis mucosa. These occurred independently of the rhythmic contractions of the muscular coat. Eisler and Link (1921) were able to demonstrate these folds in all normal and most abnormal cases. The exceptions were cases of marked dilatation of the stomach, with excessive hypersecretion, and where infiltrations of the stomach had produced destruction of the mucous membrane.

Schwarz (1908), in order to be certain that the entire stomach, including the pylorus, was completely filled by means of the opaque mixture, determined that the best means of doing this was by demonstrating the presence of the bismuth beyond the confines of the stomach itself. Such evidence would enable the investigator to study the pylorus in its entirety and to prove the absence of obstruction at the pyloric outlet. By working along this line he succeeded in showing the duodenum roentgenographically. He stated that while the first portion of the duodenum could be well filled, the bismuth passed rapidly through the descending and horizontal parts. He also made the highly significant and accurate statement that this first portion of the duodenum was almost the exclusive location for peptic ulcer of the duodenum.

Percy Brown (1933) summarized the foregoing review with these words: "With such a prelude as to alimentary visceral topography, to be amplified soon and later by Cole, Mills, Carman, Le Wald and others, was ushered in the more detailed radiology of the digestive structures, and the field became a lodestone of attraction for the new compass-needle of discovery."

In this field at least two schools of thought and practice developed, one was essential to that of the other, and both to the advancement of roentgenology. One was basically roentgenoscopic (fluoroscopic observation) and depended upon its radiographic records for confirmation. The other founded its diagnostic opinion upon the direct evidence of disease as shown graphically in repeated or seriated exposure records.

Carefully compiled and accurately checked records are available to prove the efficiency of the combined roentgenoscopic and roentgenographic method. A study of these records also reveals that there still remains a field for investigation by other methods with potentials beyond those of the roentgenologic method.

In the successive years of the most recent decade 17% of the total number of patients registered in The Mayo Clinic had symptoms bebecause of which they were sent for roentgenologic study of the esophagus, stomach and duodenum. The roentgenologic findings were negative in 11.3% of the total registration (66.3% of those examined). Approximately 7% of the patients with negative roentgenologic findings had surgical investigation for biliary or other tract lesions, many of which frequently produce reflex symptoms in the stomach. In the remaining 59.3% of examined patients showing negative findings the inference remained that their symptoms were due to some reflex cause or some functional disorder; this group would seem to offer the most fertile field for further investigation by such a method as gastroscopy.

The announcement of the Wolf-Schindler flexible gastroscope in 1932 revived interest in attempts to diagnose lesions of the stomach by direct visualization. The flexibility of this new instrument, invented by Schindler, made the procedure relatively easy and safe. Heretofore most physicians felt that the results obtained did not justify the difficulties and the dangers encountered in passing the instrument.

The consensus expressed in this symposium was that the chief value of gastroscopy was in the study of the finer changes in the gastric mucosa; its greatest value probably being in the recognition of chronic gastritis, a definite disease entity in which the changes in the mucosa are smaller than in ulcer and cancer, and, therefore, less easily recognized by Roentgen ray examination. The gastroscopic appearances of hypertrophic gastritis, chronic gastritis with ulcerating erosions and atrophic gastritis were described and said to be typical.

Schindler stated that in most cases the roentgenogram of the gastric mucosa bears little resemblance to the pattern seen by the gastroscopist, and sometimes changes clearly demonstrable at repeated gastroscopic examinations may be entirely imperceptible to the roentgenologist. Conversely, the roentgenologist sometimes sees changes that are invisible to the gastroscopist. He considered gastroscopy as best suited to the study of the mucosa, roentgenology best suited to the study of the gastric tissues.

In Schatzki's experience, a discrepancy between Roentgen findings and gastroscopy was rather rare when changes typical of hypertrophic gastritis were demonstrated by Roentgen examination. The converse was much more common. A large number of patients with an appearance of hypertrophic gastritis by gastroscopy showed a normal Roentgen picture. The changes in these cases apparently involved the mucosa more than the submucosa. Mucosal relief studies by the Roentgen

method may suggest a normal stomach where gastroscopy will reveal marked atrophy. Ulcerative gastritis is characterized by shallow superficial erosions; the shallowness of the erosions and the marked degree of accompanying gastric secretion usually prevents demonstration of this lesion by the Roentgen method.

Schatzki summarized the advantages and disadvantages of both methods as he had observed them from the standpoint of the roentgenologist in 7 years' close coöperation with gastroscopists. Gastroscopy is by far the best method of examination for gastritis. It is done with precise instruments, such as lenses and mirrors, giving the same optical impression as the naked eye. It is even superior, as it gives a slightly magnified image. Another advantage of gastroscopy is the ability to see colors; additional help is afforded where differences in color are a factor in the making of a diagnosis. The Roentgen examination, on the other hand, is easier to make, less dangerous, and therefore more suited to routine investigation. It is possible to demonstrate all portions of the stomach by the Roentgen method, whereas it is difficult, sometimes even impossible, to see parts of the fundus or the lesser curvature of the antrum by gastroscopy. The routine observation of peristalsis of the whole stomach and the impression obtained by manual palpation which gives information concerning flexibility or rigidity of the wall lend an important advantage to the Roentgen method. Both methods may be combined to advantage in the control gastroscopic examination of the surrounding surfaces and of the crater base to decide the question of malignancy in some ulcers. Gastroscopy is superior in the observation of the final healing of the mucosa in gastric ulcers. In the differential diagnosis between hypertrophic gastritis and diffuse cancerous or lymphomatous infiltrations gastroscopic examination may be an important factor in the final decision. Finally, it is worthwhile to mention that gastroscopic control may correct obvious mistakes in Roentgen ray examination and interpretation.

Kirklin, while welcoming any method that would disclose and identify lesions that escape roentgenologic revelation and recognition, considered the margin of potential improvement to be narrow. The gross lesions, including the advanced cancers and benign new growths, have such striking roentgenologic characteristics, demonstrable even by the simplest technique, that few errors in diagnosis are permissible. The study of the mucosal pattern has long been a part of the standard routine of roentgenoscopy and by it any gastric lesion, whether ulcerative or tumefactive, that visibly alters the internal topography of the stomach is demonstrable even when the diameter of the lesion is only a few millimeters, and any failure to find it should be charged against the examiner and not against the method. Inspection of the duodenal bulb is an essential feature of the gastric examination and cannot be effected with the gastroscope. Gastroscopy as a routine in examination of the stomach will not be warranted until it has been shown conclusively that it is more uniformly accurate in diagnosis than roentgenoscopy and is attended with as little risk to the patient. When medical roentgenology was new it suffered from the enthusiastic claims of its ardent practitioners and its progress was retarded. It was to be hoped that this history would not be repeated in the case of gastroscopy.

CHARLES G. SUTHERLAND, M.D.

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PHYSIOLOGY

PROCEEDINGS OF
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The Effect of Diet Upon Host Resistance to Enteritidis Infection. CHARLES F. CHURCH, CLAIRE FOSTER, and DOROTHY W. ASHER (Department of Pediatrics, University of Pennsylvania, and the Children's Hospital of Philadelphia). The survival curves of groups of mice inoculated with a strain of *Salmonella enteritidis* by stomach tube were reproducible and showed no variation beyond normal statistical error, provided the following conditions were uniform: (1) genetic background; (2) physical environment; (3) diet. Variation in any one of these factors may result in altered survival.

The distribution of the infecting organism in the tissues of mice on the same diet was found to be essentially the same whether the host was of the A-line (90% survival) or the D-line (30% survival). The parasite was found in cultures of the mesenteric glands of both lines, on the second day after inoculation, and successively invaded the spleen, axillary and submaxillary lymph nodes, liver and kidney. The organism was recovered from the heart in 4 out of 20 A-mice and in 5 out of 20 D-mice.

The Steenbock diet and the Sherman diet were found almost equally satisfactory for growth and reproduction of D-mice. However, progenies from mothers on the Steenbock diet showed consistently higher survival following inoculation than progenies from mothers on the Sherman diet. This difference persisted when the young from two maternal diets were changed to the same purified diet beginning 2 weeks before inoculation. Changing the progeny at weaning from the Steenbock to the Sherman diet did not diminish resistance. The diet of the mother during pregnancy and lactation thus appears to be a factor of great importance in influencing the survival of the offspring on exposure to risk of infection.

The Action of Cyanide and of Oxygen Lack on Glomerular Function in the Perfused Frog's Kidney. L. V. BECK and A. N. RICHARDS (Laboratory of Pharmacology, University of Pennsylvania). The

oliguria frequently produced in the surviving frog's kidney by arterial perfusion with cyanide-Ringer or with oxygen-free Ringer is, as a rule, not accompanied by a corresponding decrease in arterial perfusion flow. This phenomenon, ascribed by some to depression of secretory processes in the glomerular membrane, has been made the basis of their belief that glomerular urine is a secretion and not a filtrate. Our experiments, like those of Adolph on asphyxia, indicate that arterial vessels which supply glomeruli are constricted by CN or O_2-lack whereas extra-renal vessels (*e. g.*, lumbar arteries, ureteral branches of the urogenital arteries) simultaneously perfused, are not constricted or are dilated. In consequence, glomerular perfusion and glomerular capillary pressure may be decreased by these agencies without corresponding decrease in total arterial perfusion flow and the phenomenon referred to is not inconsistent with the doctrine of glomerular filtration.

Experiments on Water Diuresis. ARTHUR M. WALKER (Laboratory of Pharmacology, University of Pennsylvania). The experiments concerned themselves with the theory that alterations in urine volume are dictated by changes in the production of an antidiuretic hormone by the posterior lobe of the pituitary gland. The results of the experiments were not such as to substantiate the theory.

1. It was found that completely pituitarectomized cats and rats respond to forced water administration and water deprivation by changes in urine volume which are very comparable to those exhibited by the same animals before operation.

2. Gilman and Goodman's finding of an antidiuretic substance in the urine of dehydrated rats (*J. Physiol.*, **90**, 371, 1937) is confirmed; but the incompleteness with which rats excrete injected pituitrin, the relative instability of pituitrin in rat urine at pH exceeding 5.0, and the ease with which pituitrin dialyzes out of thin cellophane membranes argue against the substance being derived from the pituitary gland. Further, a similar antidiuretic substance has been found in the urine of pituitarectomized rats and cats and of hydrated rats, cats and rabbits.

3. The subcutaneous injection of water into rats produces a diuresis quantitatively similar to that produced by the oral administration of water in similar amounts. The subcutaneous injection of hypertonic sodium chloride solutions delays or arrests a water diuresis; this antidiuretic effect is shared to some extent by hypertonic glucose solutions but not by solutions of urea, potassium chloride, or sodium chloride.

Localization and Physiological Significance of the Aortic Chemoreceptors in the Dog. JULIUS H. COMROE, JR., and WILLIAM H. F. ADDISON (Laboratories of Pharmacology and Anatomy, University of Pennsylvania). Comparison of the effects of anoxia (produced by N_2O inhalation, intravenous cyanide and lobeline) upon respiration and circulation before and after carotid denervation in 48 dogs showed: (*a*) the intense hyperpnea always produced by these agents was greatly reduced after carotid denervation in 61%; moderately reduced in 28%; only slightly reduced in 11%; (*b*) the hypertension produced by these agents however was invariably intensified after carotid denervation.

This residual hyperpnea and marked hypertension were always abolished by subsequent vagotomy. Even if the carotid innervation was intact, vagotomy alone usually abolished the hypertension produced by anoxia. Therefore, though the hyperpnea of anoxia is produced mainly by carotid body reflexes (and to a lesser extent, aortic body reflexes), the hypertension of anoxia is produced by reflexes arising chiefly in the aortic, and to a lesser extent in the carotid, chemoreceptors. The latter exceptionally produce marked reflex hypertension, but only if the opposing reflex bradycardia is eliminated by vagotomy.

By means of intraäortic injections of lobeline and cyanide, after carotid denervation, the aortic chemoreceptors were localized in the Aortic Body (*Paraganglion Aorticum Supracardiale*). This body (similar in structure to the carotid body) lies on the dorsocaudal aspect of the ascending aorta at the level of the brachiocephalic orifice, and receives blood directly from a short aortic branch. The afferent nervous pathways are over both vagodepressors; electrical stimulation of the fibers to the right vagus reproduces the typical aortic body response —marked hypertension and hyperpnea (similar to that produced by intraäortic cyanide after carotid denervation). Just as the carotid body chemoreceptors are separable from the carotid sinus pressure-receptors, so the aortic body is separable from the aortic arch pressure-receptors. The McDowall reflex may be due to stimulation of the aortic body by anoxia, for these pressor impulses may be abruptly removed not only by vagotomy but frequently by oxygen inhalation.

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